Organic Reactions

Organic Reactions

VOLUME IX

JOHN WILEY & SONS, INC.

New York · London · Sydney

/

PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the investigator will be able

to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

CONTENTS

SUBJECTS OF PREVIOUS VOLUMES

CHAPTER 1

THE CLEAVAGE OF NON-ENOLIZABLE KETONES WITH SODIUM AMIDE. THE HALLER-BAUER REACTION

K. E. HAMLIN AND ARTHUR W. WESTON

Abbott Laboratories

CONTENTS

1

INTRODUCTION

In this chapter the Haller-Bauer reaction is defined as the action of sodium amide on a non-enolizable ketone causing cleavage of a carbon to carbon bond and resulting in the formation of an amide and a hydrocarbon.

$$R-C-R' \xrightarrow{\text{NaNH}_2} RCONH_2 + R'H$$
$$O$$
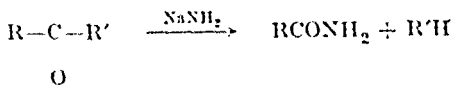
Textbook definitions of the Haller-Bauer reaction have limited it to the alkylation of ketones in which sodium amide acts as a condensing agent[1,2] or have considered it a combination of the alkylation and cleavage reactions.[3]

The cleavage of ketones by sodium amide was discovered in 1906 by Semmler[4] in connection with his investigations of the structure of fenchone. Suspecting that fenchone contained no α-hydrogen atoms, Semmler chose sodium amide as a reagent that might effect a cleavage without causing rearrangement of the molecule. As a result, the sodio derivative of fencholic acid amide was obtained. He did not explore the potentialities of the reaction. This was done by Haller and Bauer,[5] who in 1908 reported the isolation of benzamide after the treatment of benzo-phenone with sodium amide in boiling benzene or toluene and who followed this observation with an extended study of the reaction.

A modification of the Haller-Bauer reaction involving the use of a fused eutectic mixture of sodium and potassium amides[6] has been applied to certain alicyclic and bicyclic terpenoid ketones as well as to some amides. The carbonyl group was completely eliminated from these compounds. For example, fenchone was cleaved to 1-methyl-3-isopropylcyclopentane, and 1-benzoylpiperidine gave rise to benzene and piperidine.

MECHANISM

On the basis of their early experiments, Haller and Bauer proposed a mechanism for the reaction of sodium amide with benzophenone which involved a preliminary addition to the ketone.[5] The "sodium salt of

[1] Cohen, *Organic Chemistry for Advanced Students*, I, 4th ed., p. 217, Longmans, Green and Co., New York, 1924.

[2] Degering, *An Outline of Organic Chemistry*, 4th ed., p. 321, Barnes and Noble, 1941.

[3] *The Merck Index*, 6th ed., p. 1055, Merck and Co., Rahway, N.J., 1952.

[4] Semmler, *Ber.*, **39**, 2577 (1906).

[5] Haller and Bauer, *Compt. rend.*, **147**, 824 (1908).

[6] Freidlin, Balandin, and Lebedova, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, **1941**, 167 [*C. A.*, **37**, 3749 (1943)].

diphenylaminocarbinol" (I) thus formed could be isolated as a crystalline

$$C_6H_5COC_6H_5 + NaNH_2 \rightarrow C_6H_5-\underset{\underset{NH_2}{|}}{\overset{\overset{ONa}{|}}{C}}-C_6H_5$$

I

$$C_6H_5-\underset{\underset{NH_2}{|}}{\overset{\overset{ONa}{|}}{C}}-C_6H_5 + H_2O \rightarrow C_6H_5CONH_2 + C_6H_6 + NaOH$$
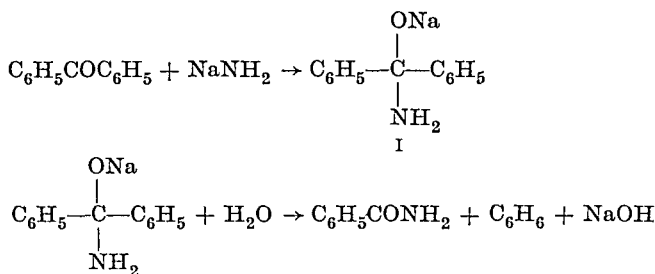
product. Upon treatment with water it gave rise to benzamide and benzene. In 1922 Haller published a review article and repeated his ideas on the mechanism of the reaction.[7]

Schönberg in 1924 and 1925 described his researches on the action of sodium amide on diaryl ketones.[8,9] His observations with benzophenone were in agreement with those of Haller and Bauer; his interpretation of the reaction, however, differed from theirs as far as the decomposition of the adduct I was concerned. It was Schönberg's view that the addition product I undergoes thermal cleavage in boiling benzene or toluene to furnish benzene and the sodio derivative of benzamide,[10] which can be isolated from the reaction mixture. Treatment with water hydrolyzes *this latter* sodio derivative to benzamide.

$$C_6H_5-\underset{\underset{NH_2}{|}}{\overset{\overset{ONa}{|}}{C}}-C_6H_5 \xrightarrow{\text{Heat}} C_6H_6 + C_6H_5-\overset{\overset{O}{||}}{C}-NHNa \text{ or } C_6H_5-\overset{\overset{ONa}{|}}{C}=NH$$

I

$$C_6H_5CONHNa + H_2O \rightarrow C_6H_5CONH_2 + NaOH$$
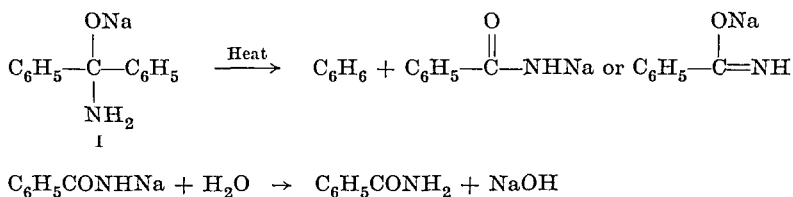
Further evidence to support this mechanism was provided by the reaction of *p*-phenylbenzophenone with sodium amide. When these materials were heated under refluxing conditions in dry toluene and the solid so formed was removed by filtration, biphenyl was isolated from the filtrate. As both the hydrocarbon and the sodio derivative of the amide were formed in the absence of water it was evident that water was not necessary for the formation of the hydrocarbon. Lea and Robinson[11] have carried out additional experiments on the action of sodium amide

[7] Haller, *Bull. soc. chim. France*, [4] **31**, 1117 (1922).

[8] Schönberg, Abelsdorff, Kirchrath, Malchov, and Rosen, *Ann.*, **436**, 205 (1924).

[9] Schönberg, *Ber.*, **58**, 580 (1925).

[10] Curtius, *Ber.*, **23**, 3038 (1890).

[11] Lea and Robinson, *J. Chem. Soc.*, **1926**, 2351.

on unsymmetrical benzophenones. Their description of the reaction mechanism is in full agreement with that of Schönberg.

A modern interpretation of the reaction might be written as follows:

$$\text{RCOR}' + \text{NH}_2^- \rightleftharpoons R-\underset{\underset{\text{NH}_2}{|}}{\overset{\overset{\text{O}^-}{|}}{C}}-R' \rightleftharpoons R^{\bar{:}} + \text{H}_2\text{NCOR}' \rightarrow \text{RH} + (\overline{\text{H}}\text{NCOR}')$$
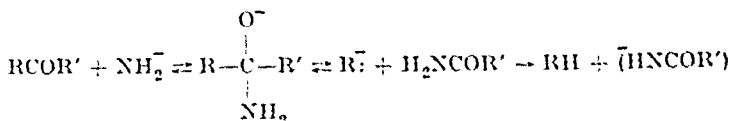
The direction of cleavage depends upon the relative electronegativities of R and R'. If R' in the ketone, RCOR', is more strongly electron repelling than R the primary product is $R'CONH_2$.

The mechanism suggested by Freidlin[6] for the modification of the Haller-Bauer reaction in which a fused eutectic mixture of sodium and potassium amides reacts with a ketone or an amide is given below. Cleavage occurs to eliminate the carbonyl group with the formation of metal cyanamides.

$$\text{RCOR}' \xrightarrow{\text{NaNH}_2} \text{RR'C(OH)NHNa} \rightarrow R'\text{H} + \text{RCONHNa}$$

$$\text{RCONHNa} \xrightarrow{\text{NaNH}_2} \text{RC(OH)(NHNa)}_2 \rightarrow \text{RH} + (\text{NaHN})_2\text{CO}$$

$$(\text{NaHN})_2\text{CO} \longrightarrow \text{Na}_2\text{CN}_2 + \text{H}_2\text{O}$$
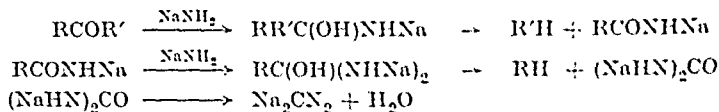
SCOPE AND LIMITATIONS

The Haller-Bauer reaction has been applied to many non-enolizable ketones[12] and with certain classes of these compounds has considerable synthetic utility. It is one of the few general methods for the synthesis of tertiary carboxamides, compounds which are useful as intermediates for tertiary carboxylic acids or tertiary carbinamines. By hydrolysis of the amides,[13] many tertiary carboxylic acids have been made available, and an even less accessible class of compounds, the tertiary carbinamines, can be formed by application of the Hofmann, Schmidt, and Curtius reactions to the amides or acids.[14]

$$R-\underset{\underset{R''}{|}}{\overset{\overset{R'}{|}}{C}}-\underset{}{\overset{\overset{O}{\|}}{C}}-R''' \xrightarrow{\text{NaNH}_2} R-\underset{\underset{R''}{|}}{\overset{\overset{R'}{|}}{C}}-\text{CONH}_2 \longrightarrow R-\underset{\underset{R''}{|}}{\overset{\overset{R'}{|}}{C}}-\text{CO}_2\text{H}$$

$$R-\underset{\underset{R''}{|}}{\overset{\overset{R'}{|}}{C}}-\text{NH}_2$$

---
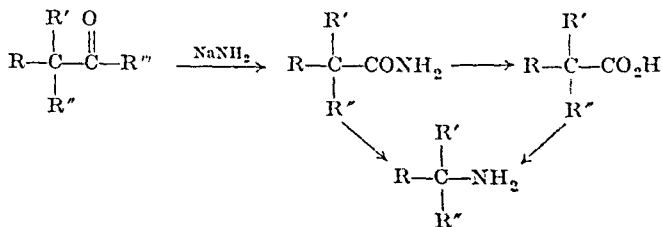
[12] A few ketones having an α-hydrogen atom have been cleaved by sodium amide during attempted alkylation. Some of these cleavages are considered on pp. 8 and 12; all are cited in Table I.

[13] Sperber, Papa, and Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948).

[14] *Organic Reactions*, Vol. III, Chapters 7, 8, and 9, John Wiley & Sons, New York, 1946.

The Cleavage of Aliphatic or Alicyclic Phenyl Ketones (Table I)

The most important application of the Haller-Bauer reaction is the cleavage of aliphatic or alicyclic phenyl ketones. Broadly, the cleavage occurs in such a way as to produce the tertiary carboxamides. For example, α,α-dimethylpropiophenone when heated in benzene under refluxing conditions with sodium amide affords a nearly quantitative yield of pivalamide. Similarly, 1-methylcyclohexyl phenyl ketone under the same conditions readily forms 1-methylcyclohexanecarboxamide in 88% yield. Since the starting ketones in general are rather easily obtained, the reaction has found considerable application.

When two of the substituents (for example, R and R′) of a trialkylacetophenone II are methyl, the third (R″) may be increased in size to C_{18} without interfering with the normal direction of the reaction. On the

$$
\begin{array}{ccc}
\overset{\displaystyle R}{\underset{\displaystyle R''}{\overset{|}{\underset{|}{R'-C-}}}}\overset{\displaystyle}{\underset{\displaystyle O}{\overset{|}{\underset{\|}{C-}}}}C_6H_5 & \rightarrow & \overset{\displaystyle R}{\underset{\displaystyle R''}{\overset{|}{\underset{|}{R'-C-}}}}\overset{\displaystyle}{\underset{\displaystyle O}{\overset{|}{\underset{\|}{C-}}}}NH_2 \\
\text{II} & &
\end{array}
$$
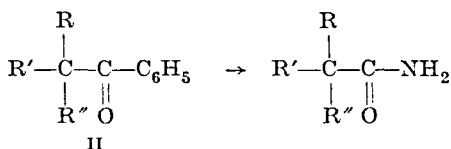
other hand, as R and R′ increase in size and complexity, the yields of trialkylacetamides fall off rapidly and the amount of benzamide increases. This effect was studied in detail by restricting one alkyl group to methyl or ethyl and progressively increasing in size the other two.[15] No difficulty was experienced in the preparation of variously branched amides containing up to ten carbon atoms. However, in II, where R, R′, and R″ total eleven carbon atoms, certain irregularities became evident and more benzamide resulted. For example, α-methyl-α-n-butyl-n-hexamide and α-ethyl-α-n-propyl-n-hexamide were formed readily. On the other hand, α-methyl-α-ethyl-n-octamide was obtained in an impure state while α,α-diethylheptamide could not be isolated. With a total of twelve or more carbon atoms in the three substituent groups, the molecules exhibited even greater variation from the normal direction of cleavage. The investigators concluded that failure of the method might be expected with alkyl phenyl ketones of relatively low molecular weight where the three substituents are highly complex.

The results of these workers may be explained partly on the basis of steric hindrance: the more complex the branching about the carbonyl group, the less successful is the cleavage. Recovery of some starting ketone from the reaction mixture is possible with such compounds. However, the isolation of increasing amounts of benzamide indicates that some attack on the carbonyl group occurs.

[15] Carter and Slater, *J. Chem. Soc.*, **1946**, 130.

The application of Newman's "Rule of Six"[16] to account for the steric effects of branching about the carbonyl group is only partly satisfactory. The results are neither strikingly in agreement nor strikingly in disagreement with the rule.

The cleavage of alicyclic phenyl ketones by their reaction with sodium amide[17–21] follows the direction reported for alkyl phenyl ketones. Good yields of the expected 1-alkyl alicyclic carboxamides were obtained with little evidence of benzamide where the alkyl substituent (R) was methyl, ethyl, n-propyl, isopropyl, or n-butyl.

$$(CH_2)_nC \overset{R}{\underset{COC_6H_5}{\Big<}}$$
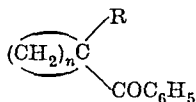
Anomalous results were reported with 1-methylcyclopropyl phenyl ketone, which furnished benzamide and no 1-methylcyclopropanecarboxamide.[17]   On the other hand, replacement of methyl by benzyl changed the direction of cleavage and 1-benzylcyclopropanecarboxamide was obtained readily.   This cleavage of 1-benzylcyclopropyl phenyl ketone in the expected manner was confirmed by the hydrolysis of the amide and identification of the 1-benzylcyclopropanecarboxylic acid.[20]

Diketones of type III provide an excellent source of $\alpha,\alpha,\alpha',\alpha'$-tetra-alkyldiamides.   The diketones, where R is methyl and n has been varied from 3 to 14, have been converted to diamides.[22–24]

$$C_6H_5C\overset{R}{\underset{O}{\underset{|}{\overset{|}{C}}}}(CH_2)_n\overset{R}{\underset{O}{\underset{|}{\overset{|}{C}}}}CC_6H_5 \xrightarrow{\text{NaNH}_2} H_2NC\overset{O}{\underset{R}{\underset{|}{\overset{\|}{C}}}}(CH_2)_n\overset{R}{\underset{R}{\underset{|}{\overset{|}{C}}}}CNH_2$$

III
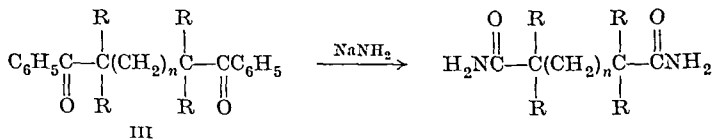
The reaction also proceeds in the expected manner with diketones such as IV, synthesized by use of a dihalide containing a benzene nucleus.   The corresponding *ortho* and *meta* derivatives were also prepared.[25]

[16] Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950).

[17] Haller and Benoist, *Ann. chim. Paris*, [9] **17**, 25 (1921).

[18] Wash, Shive, and Lochte, *J. Am. Chem. Soc.*, **63**, 2975 (1941).

[19] Hamlin and Freifelder, *J. Am. Chem. Soc.*, **75**, 369 (1953).

[20] Piehl and Brown, *J. Am. Chem. Soc.*, **75**, 5023 (1953).

[21] Hamlin and Biermacher, *J. Am. Chem. Soc.*, **77**, 6376 (1955).

[22] Haller and Bauer, *Compt. rend.*, **152**, 1638 (1911).

[23] Adams and Anderson, *J. Am. Chem. Soc.*, **73**, 136 (1951).

[24] Leonard and Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).

[25] Dumesnil, *Ann. chim. Paris*, [9] **8**, 70 (1917).

$$C_6H_5\underset{\underset{O}{\parallel}}{\overset{\overset{CH_3}{|}}{C}}\overset{\overset{}{|}}{\underset{CH_3}{\underset{|}{C}}}CH_2\!\!-\!\!\langle\text{arene}\rangle\!\!-\!\!CH_2\!\!-\!\!\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}\!\!-\!\!\underset{O}{\underset{\parallel}{CC_6H_5}} \xrightarrow{\text{NaNH}_2}$$

IV

$$H_2N\underset{}{\overset{\overset{O}{\parallel}}{C}}\!\!-\!\!\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}\!\!-\!\!CH_2\!\!-\!\!\langle\text{arene}\rangle\!\!-\!\!CH_2\!\!-\!\!\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}\!\!-\!\!\underset{\overset{O}{\parallel}}{C}NH_2$$
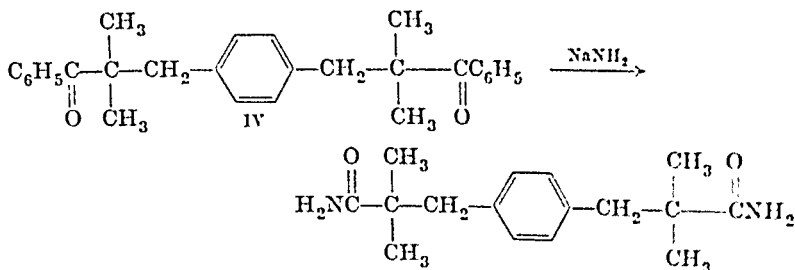
An interesting secondary reaction is encountered in a series of 1,1-dialkyl-3-butenyl phenyl ketones (V). These ketones on treatment with sodium amide yield unsaturated amides which cyclize to the corresponding pyrrolidones (VI). Brown and van Gulick[26] conclusively proved that for

$$CH_2\!\!=\!\!CHCH_2\!\!-\!\!\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}}\!\!-\!\!\underset{\overset{O}{\parallel}}{C}C_6H_5 \rightarrow \begin{array}{c} CH_2\!\!-\!\!CR_2 \\ | \qquad | \\ H_3CCH \quad C\!\!=\!\!O \\ \diagdown N \diagup \\ | \\ H \end{array}$$

V   VI
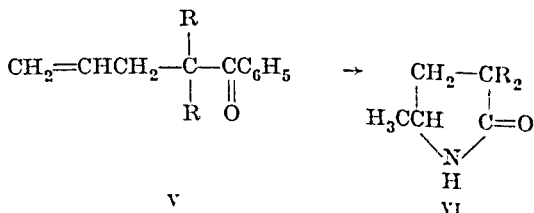
3,3,5-trimethyl-2-pyrrolidone the reaction takes the course proposed by Haller and Bauer,[27] viz., the 2,2-dimethyl-4-pentenamide arising from the sodium amide cleavage of 1,1-dimethyl-3-butenyl phenyl ketone will cyclize under basic conditions.

$$CH_2\!\!=\!\!CHCH_2C(CH_3)_2COC_6H_5 \xrightarrow{\text{NaNH}_2}$$

$$[CH_2\!\!=\!\!CHCH_2C(CH_3)_2CONH_2] \rightarrow \begin{array}{c} CH_2\!\!-\!\!C(CH_3)_2 \\ | \qquad | \\ H_3CCH \quad C\!\!=\!\!O \\ \diagdown N \diagup \\ | \\ H \end{array}$$
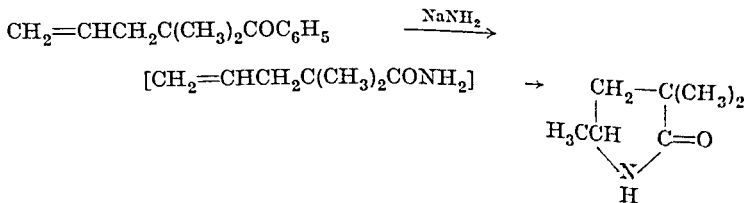
Several 5-methyl-3,3-dialkyl-2-pyrrolidones have been prepared by this method, and the reaction is considered to be general.[28]

Most aralkyl and heterocyclic-alkyl phenyl ketones on treatment with sodium amide give the expected substituted alkylacetamides (Table I). However, α,α-dimethyl-γ,δ-epoxybutyl phenyl ketone is not attacked.[29]

The synthetic utility of the Haller-Bauer reaction is limited by the unavailability of the starting ketones. The simpler ketones are readily obtained by the alkylation of various acetophenones by conventional

[26] Brown and van Gulick, *J. Am. Chem. Soc.*, **77**, 1092 (1955).

[27] Haller and Bauer, *Compt. rend.*, **158**, 1086 (1914).

[28] Haller and Bauer, *Compt. rend.*, **160**, 541 (1915).

[29] Ramart-Lucas and Haller, *Compt. rend.*, **158**, 1302 (1914).

methods. The introduction of the third group into ketones of high molecular weight is restricted by steric effects. Such alkylations become progressively more difficult as the size of the entering group becomes larger; this is a major drawback to the use of the method for synthesis of acids containing a quaternary carbon atom.[30] Thus, it is impossible to methylate ω,ω-di-n-decylacetophenone. This barrier to the synthesis of trialkylacetophenones in which two substituents are long chain can be obviated by introducing the small group first into a higher homolog of acetophenone and then replacing the tertiary hydrogen by a long-chain alkyl group.[15]

Attempts to introduce an alkyl group in the tertiary position of an alicyclic phenyl ketone sometimes gave anomalous results. Alkylation of 2-methylcyclopentyl phenyl ketone was usually normal, but if the ketone was allowed to react with sodium amide in boiling xylene and then treated with isopropyl iodide a mixture of 2-methylcyclopentanecarboxamide, N-isopropyl-2-methylcyclopentanecarboxamide, and the isopropyl ether of the enol form of the parent ketone resulted.[18,19] Cleavage of this
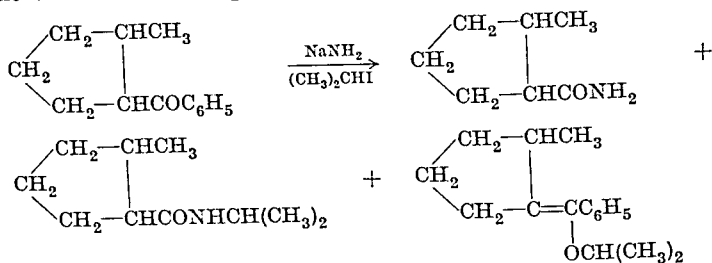
ketone, containing an α-hydrogen atom, was occurring in place of alkylation. The cleavage of cyclohexyl phenyl ketone by sodium amide resulted in a 1% yield of cyclohexanecarboxamide.[19] Similarly cyclopropyl phenyl ketone with sodium amide in boiling benzene gave a 42% yield of cyclopropanecarboxamide as well as a small amount (2%) of benzamide. These results could not be repeated and do not coincide with those previously reported that, with sodium amide in moist benzene, benzamide was the only product isolated.[17]

The Cleavage of Aliphatic Ketones (Table II)

Symmetrically substituted acetones react with sodium amide to form the predicted tertiary carboxamide and trialkylated methane.[31] Thus hexamethylacetone gives an excellent yield of pivalamide by this method.

[30] Birch and Robinson, J. Chem. Soc., 1942, 488.
[31] Haller and Bauer, Compt. rend., 150, 664 (1910).

On the other hand, a mixture of the four possible products (two amides and two hydrocarbons) is obtained from 2,2,4,4-tetramethyl-3-hexanone (VII).

$$
\begin{array}{ccc}
& CH_3 \quad O \quad\; CH_3 & \\
& |\qquad\;\; || \qquad\; | & \\
CH_3\!-\!\!\!\!\! & C\!\!-\!\!\!-\!\!C\!\!-\!\!\!-\!\!C\!\!-\!\!CH_2CH_3 & \\
& |\qquad\qquad\;\; | & \\
& CH_3 \qquad\;\; CH_3 & \\
& \text{VII} &
\end{array}
\qquad
\begin{array}{ccc}
& CH_3 \quad O \quad\; CH_3 & \\
& |\qquad\;\; || \qquad\; | & \\
CH_3\!-\!\!\!\!\! & C\!\!-\!\!\!-\!\!C\!\!-\!\!\!-\!\!C\!\!-\!\!CH_2C_6H_5 & \\
& |\qquad\qquad\;\; | & \\
& CH_3 \qquad\;\; CH_3 & \\
& \text{VIII} &
\end{array}
$$

$$
\begin{array}{ccc}
& CH_3 \quad O \quad\; C_2H_5 & \\
& |\qquad\;\; || \qquad\; | & \\
CH_3\!-\!\!\!\!\! & C\!\!-\!\!\!-\!\!C\!\!-\!\!\!-\!\!C\!\!-\!\!CH_2CH_3 & \\
& |\qquad\qquad\;\; | & \\
& CH_3 \qquad\;\; C_2H_5 & \\
& \text{IX} &
\end{array}
\qquad
\begin{array}{ccc}
& CH_3 \quad O \quad\; CH_3 & \\
& |\qquad\;\; || \qquad\; | & \\
(CH_3)_2CH\!-\!\!\!\!\! & C\!\!-\!\!\!-\!\!C\!\!-\!\!\!-\!\!C\!\!-\!\!CH(CH_3)_2 & \\
& |\qquad\qquad\;\; | & \\
& CH_3 \qquad\;\; CH_3 & \\
& \text{X} &
\end{array}
$$
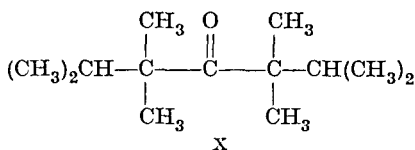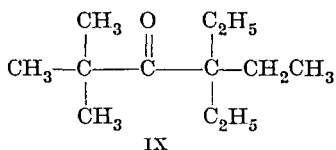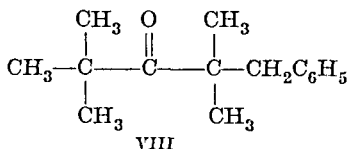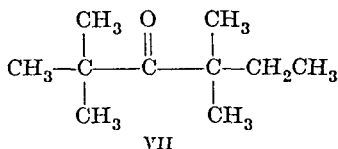
Although substituted acetones may furnish a mixture of two possible amides and two hydrocarbons, one direction of cleavage may predominate. 2,2,4,4-Tetramethyl-5-phenyl-3-pentanone (VIII) cleaves exclusively to pivalamide and isobutylbenzene;[32] 4,4-diethyl-2,2-dimethyl-3-hexanone (IX) when treated with sodium amide at the boiling point of xylene forms pivalamide and α,α,α-triethylacetamide in a 5-to-1 ratio.[31]

An additional limitation to the practical use of the reaction with aliphatic ketones is encountered when the substituents are highly branched. For instance, the ketone X is inert to the action of sodium amide under vigorous conditions.[32] Since in such cases the starting ketone is recovered, the failure of the reaction is possibly attributable to steric hindrance about the carbonyl group.

The Cleavage of Diaryl Ketones (Table III)

Diaryl ketones are readily attacked by sodium amide. If symmetrically substituted they can yield only one amide and one hydrocarbon. Unsymmetrical diaryl ketones in which the substituents cause one aromatic nucleus to be much more strongly electron donating than the other give predominantly one amide and one hydrocarbon.

From the large number of diaryl ketones falling between these two extremes, four possible products, two amides and two hydrocarbons, are formed in varying amounts. Only the first two types of diaryl ketones are useful for the preparation of amides.

Schönberg[8,9] and Lea and Robinson[11] cleaved a variety of unsymmetrical diaryl ketones and determined the comparative yields of the various

---

[32] Haller and Bauer, *Ann. chim. Paris*, [9] **1**, 5 (1914).

benzamides or benzoic acids. They and, later, de Ceuster[33] drew the conclusion illustrated below that the presence of an electron-supplying group favors cleavage to produce the substituted benzamide. The same substituent in an *ortho* position results in almost complete cleavage to yield the unsubstituted benzamide; e.g., 2-methoxybenzophenone furnishes benzamide almost exclusively.
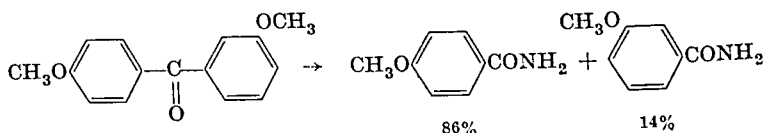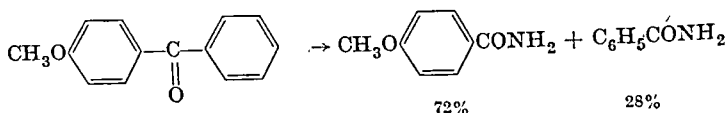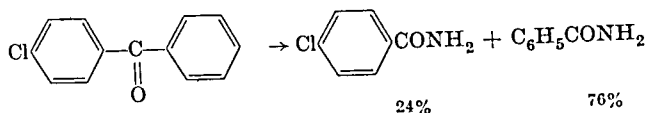
The effect of conditions upon the Haller-Bauer reaction may be illustrated by the action of sodium amide on α-naphthyl phenyl ketone.[34] On heating in benzene under refluxing conditions, only traces of benzamide were found and nearly all the original ketone was recovered. When the ketone and amide were heated under refluxing conditions in toluene for five hours, considerable benzamide was found along with ketone. When the ketone and sodium amide were heated with benzene in a sealed tube for twelve hours, the major product was benzamide accompanied by traces of naphthalene. In contrast, the isomeric β-naphthyl phenyl ketone on treatment with sodium amide in benzene cleaved readily to afford β-naphthamide as the main product along with small amounts of benzamide.[9,34]

Examples of the action of sodium amide on cyclized aromatic ketones are few. Fluorenone has been shown to yield *o*-phenylbenzamide in the expected manner.[35,36] However, anthraquinone was recovered unchanged after treatment with sodium amide.[29]

[33] De Ceuster, *Natuurw. Tijdschr. Belg.*, **14**, No. 3–6, 188 (1932) [*C. A.*, **26**, 4323 (1932) *Chem. Zentr.*, **1932**, II, 1296].

[34] Lucas, *Ann. chim. et phys.*, [8] **17**, 127 (1909).

[35] Haller and Bauer, *Compt. rend.*, **147**, 824 (1908).

[36] Haller and Bauer, *Ann. chim. et phys.*, [8] **16**, 145 (1909).

The Cleavage of Alicyclic Ketones (Table IV)

Following the first use of the Haller-Bauer reaction on fenchone, sodium amide cleavage was used in elucidation of the structure of certain terpenes related to camphor.[4] Several dialkylcamphors were cleaved by sodium amide to the corresponding dialkylcampholamides.[37,38] Each ketone cleaved in one direction and gave good yields of 1,2,2-trimethyl-3-alkylcyclopentanecarboxamide.

Symmetrically substituted cyclic ketones react with opening of the ring and give rise to one product only, an aliphatic carboxamide. Thus, with 2,2,5,5-tetramethylcyclopentanone[39] (XI) cleavage proceeds as
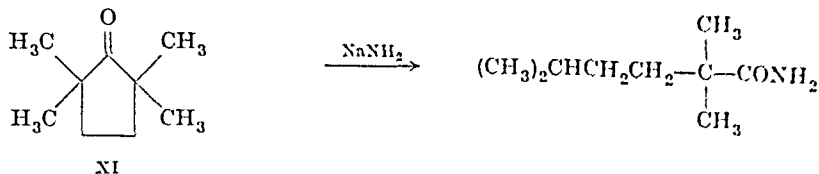
indicated. Unsymmetrically substituted cyclopentanones, however, give a mixture of two aliphatic carboxamides, thereby limiting the usefulness of the reaction. Cyclohexanones are reported[7] to be very resistant to the action of sodium amide.

The Action of Sodium Amide upon Miscellaneous Carbonyl Compounds (Table V)

Other types of carbonyl compounds have been treated with sodium amide under similar conditions. Aromatic aldehydes undergo the Cannizzaro reaction to yield the corresponding alcohol and acid.[40,41] Benzil and substituted benzils give a typical benzilic acid rearrangement.[41,42] An interesting exception is the reaction of acenaphthadione, which cleaves to oxamide and naphthalene. α-Phenylbenzoin reacts with sodium amide; both the expected products, benzilamide and benzamide, are formed, although the latter predominates.[8]

$$C_6H_5C(CH_2)_4CC_6H_5 \xrightarrow[\text{Benzene}]{NaNH_2}$$

with the two carbonyl groups shown below.

$$\underset{XII}{\begin{array}{c} C_6H_5 \\ | \\ C \\ / \ \\ CH_2 \ \ CCOC_6H_5 \\ | \qquad | \\ CH_2-CH_2 \end{array}} \quad + \quad \underset{XIII}{\begin{array}{c} C_6H_5 \\ \| \\ C \\ / \ \\ CH \ \ CHCOC_6H_5 \\ | \qquad | \\ CH_2-CH_2 \end{array}}$$
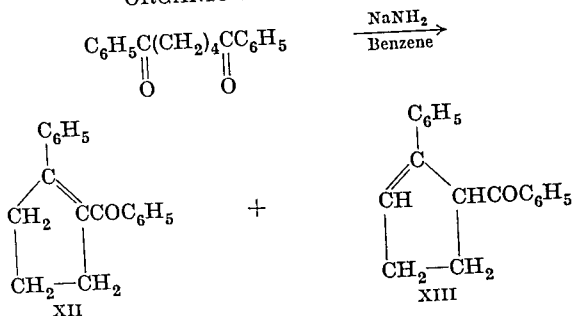
reacts in the following manner.[43] The mixture of isomers was separated and each isomer was treated with sodium amide. The lower-melting isomer undergoes the Haller-Bauer reaction and hence was assigned structure XII.[43,44] The higher-melting isomer that has an α-hydrogen does not undergo cleavage with sodium amide and hence could be designated by structure XIII or by an analogous structure in which the double bond is in another position in the ring. A parallel reaction sequence has been established for 1,7-diphenylheptane-1,7-dione.[45]

2,4-Dimethyl-1,3,5-triphenylpentane-1,5-dione (XIV), which contains α-hydrogen atoms, was cleaved with sodium amide in what appears to be a reverse Michael reaction.[46]

$$\underset{XIV}{\begin{array}{c} C_6H_5COCHCH_3 \\ | \\ CHC_6H_5 \\ | \\ C_6H_5COCHCH_3 \end{array}} \xrightarrow{NaNH_2} \underset{O}{C_6H_5CCH_2CH_3} + \underset{O}{C_6H_5CCCH_3} \overset{CHC_6H_5}{\overset{\|}{}}$$
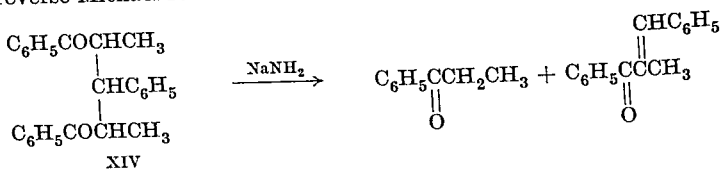
RELATED SYNTHETIC PROCESSES

Synthesis of Tertiary Carboxylic Acids. The principal alternative methods for synthesis of tertiary carboxylic acids (trisubstituted acetic acids) are briefly surveyed here. Most of the literature resulted from efforts to synthesize phthioic acid (ethyl-*n*-decyl-*n*-dodecylacetic acid) and similar structures.[30,47,48]

The aliphatic nitriles may be alkylated to the corresponding trialkylacetonitriles,[49] which may be hydrolyzed first to the amides with 80% sulfuric acid and finally to the acids. Although the difficulty of hydrolysis

[43] Bauer and Haller, *Compt. rend.*, **156**, 1470 (1913).
[44] Bauer and Haller, *Compt. rend.*, **156**, 1684 (1913).
[45] Bauer, *Ann. chim. Paris*, **1**, 343 (1914).
[46] Bauer and Haller, *Compt. rend.*, **158**, 1680 (1914).
[47] Polgar and Robinson, *J. Chem. Soc.*, **1943**, 615.
[48] Hook and Robinson, *J. Chem. Soc.*, **1944**, 152.
[49] Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

of the nitriles is a serious limitation of the method, a series of trialkyl-acetonitriles in which the alkyl groups contain as many as seven carbon atoms has been successfully hydrolyzed.[13]

Trialkylacetic acids have also been prepared by the carbonation of t-alkylmagnesium chlorides.[50] This method suffers from many disadvantages, principally the difficulty of forming Grignard reagents from tertiary alkyl halides of high molecular weight.

α-Alkylation of esters can be effected by means of sodium triphenyl-methyl and an alkyl halide.[51] However, the separation of unreacted disubstituted acetic acids or esters necessitates a tedious purification.

To a limited degree, the Favorski rearrangement of α-halogenated ketones can be used in the synthesis of tertiary carboxylic acids.[52–54] However, wherever the R groups become large or complex only metathesis occurs in the first step.

$$
\begin{array}{cccc}
\overset{R''}{\underset{Br\ \ O}{\underset{|}{R'-\overset{|}{C}-\overset{||}{C}R'''}}} & \xrightarrow{\text{NaOR}} & \overset{R''\ OR}{\underset{Br\ ONa}{R'-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-R'''}} & \rightarrow & \overset{R''\ \ OR}{R'C-\!\!\!-\!\!\!-CR'''} \quad \rightarrow \quad \overset{R''}{\underset{R'''}{R'-\overset{|}{\underset{|}{C}}-CO_2R}}
\end{array}
$$
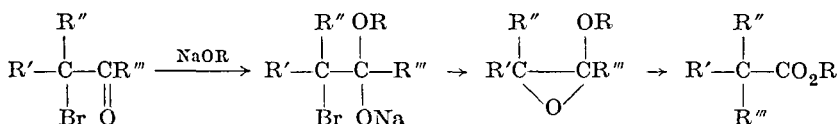
Synthesis of Tertiary Carbinamines. Synthesis of amines in which the amino group is attached to a tertiary carbon atom has been reported in only isolated instances, and in most of them the simplest member of the series, t-butylamine, was the material prepared.

A group of tertiary carbinamines has been synthesized by reaction of certain nitriles with a Grignard reagent.[55] In this fashion, alkoxyalkyl, aralkyl, or alkenyl cyanides on treatment with allylmagnesium bromide formed tertiary carbinamines in which two of the substituent groups were allyl. Hydrogenation yielded the corresponding propyl compounds.

Tertiary nitriles, prepared by alkylation of primary nitriles,[49] can be hydrolyzed to the corresponding amides. After conversion to the iso-cyanates by the Hofmann method, tertiary carbinamines can be obtained by hydrolysis.

The most important innovation in synthetic methods for the preparation of such amines is that developed by Ritter and co-workers,[56,57] in which treatment of an alkene with a nitrile in the presence of concentrated sulfuric acid produces excellent yields of amides of t-carbinamines.

[50] Whitmore and Badertscher, *J. Am. Chem. Soc.*, **55**, 1559 (1933).
[51] Hudson and Hauser, *J. Am. Chem. Soc.*, **62**, 2457 (1940).
[52] Marker and Wagner, *J. Am. Chem. Soc.*, **64**, 216 (1942).
[53] Aston, Clarke, Burgess, and Greenburg, *J. Am. Chem. Soc.*, **64**, 300 (1942).
[54] Plattner, Heusser, and Boyce, *Helv. Chim. Acta*, **31**, 603 (1948).
[55] Henze, Allen, and Leslie, *J. Am. Chem. Soc.*, **65**, 87 (1943).
[56] Ritter and Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948).
[57] Ritter and Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

When sodium cyanide is used as the nitrile, the N-alkylformamides formed can be hydrolyzed readily to the desired amines. A tertiary alcohol can be substituted for the alkene.

$$
\begin{array}{c}
\text{R} \\
\diagdown \\
\hspace{0.3em} \text{C=CHR''} \\
\diagup \\
\text{R'}
\end{array}
\xrightarrow{\text{H}_2\text{SO}_4}
\begin{array}{c}
\text{R} \\
\diagdown \\
\text{R'--C--OSO}_3\text{H} \\
\diagup \\
\text{R''CH}_2
\end{array}
$$

$$
\Big\downarrow \text{R'''CN}
$$

$$
\begin{array}{c}
\text{R} \\
\text{R'--C--NHCOR'''} \\
\diagup \\
\text{R''CH}_2
\end{array}
\longleftarrow
\begin{array}{c}
\text{R} \\
\diagdown \\
\text{R'--C--N=CR'''} \\
\diagup \hspace{1.5em} | \\
\text{R''CH}_2 \hspace{1em} \text{OSO}_3\text{H}
\end{array}
$$
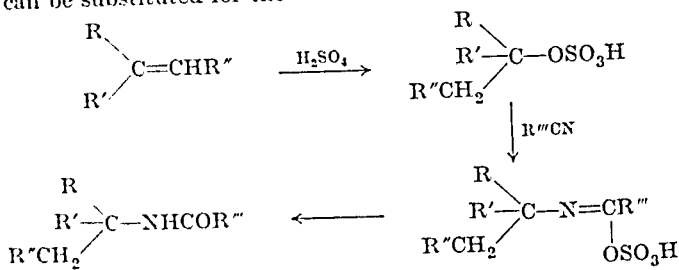
t-Butylamine has been prepared in 73% yield by the reaction of *t*-butyl-magnesium chloride with methoxyamine.[58]

EXPERIMENTAL CONDITIONS

The Haller-Bauer reaction is carried out by heating a non-enolizable ketone in an inert solvent in the presence of sodium amide. Benzene, toluene, and xylene have been used successfully. In certain instances where reaction has failed in benzene or toluene under refluxing conditions, the higher boiling temperature of xylene has led to success.

Although the quantities of sodium amide employed by various workers have varied, the use of two moles of this reagent for each carbonyl group to be cleaved is customary. Sodium amide now may be purchased, but usually it is freshly prepared in the vessel in which the reaction is to be carried out. Suitable directions for the preparation of sodium amide are found in *Organic Syntheses.*[59,60]

is continued for eight hours, and the mixture is washed with water and distilled. 2,2,9,9-Tetramethyl-1,10-diphenyldecane-1,10-dione distils at 200–265°/4–8 mm. (partial decomposition); yield 70.9 g. (75%).

A suspension of 29.25 g. (0.75 mole) of sodium amide in 600 ml. of anhydrous toluene is prepared in a 2-l. flask equipped with a stirrer, a dropping funnel, and a condenser carrying a drying tube. To the toluene-sodium amide suspension is added 70.9 g. (0.19 mole) of 2,2,9,9-tetra-methyl-1,10-diphenyldecane-1,10-dione. The mixture is heated under refluxing conditions with vigorous stirring for four hours and then cooled. After the gradual addition of 500 ml. of water, the mixture is filtered as rapidly as possible. The solid diamide thus obtained is washed with water, and the wash water is added to the filtrate. After the toluene is separated from the filtrate, the aqueous solution is concentrated. Upon acidification, this aqueous fraction yields a small additional amount of diamide. The total yield of crude $\alpha,\alpha,\alpha',\alpha'$-tetramethylsebacamide is 42 g. (87.5%). Recrystallization from ethanol results in a product melting at 210–213°.

A solution of 42 g. of crude diamide in 320 g. of concentrated sulfuric acid is cooled to 0–5° and treated with 45 g. of sodium nitrite in the minimal amount of water. The mixture is next heated to 50°, and water is added gradually with stirring. The solid acid that separates is removed by filtration, washed with water, and dissolved in aqueous sodium carbonate. The solution is decolorized with carbon, and the acid is reprecipitated with hydrochloric acid; yield 29.4 g (70%). Purification is effected by recrystallization from ethyl acetate; pure $\alpha,\alpha,\alpha',\alpha'$-tetramethylsebacic acid melts at 117–118°.

1-Methylcyclohexylamine Hydrochloride from Cyclohexyl Phenyl Ketone.[19] A suspension of 10 g. (0.25 mole) of sodium amide in 200 ml. of anhydrous toluene is prepared in a 500-ml. flask equipped with a stirrer, a dropping funnel, and a condenser carrying a drying tube. To this is added dropwise 47 g. (0.25 mole) of cyclohexyl phenyl ketone. The mixture is stirred and boiled for one hour. It is stirred and cooled in an ice bath while 71 g. (0.5 mole) of methyl iodide is added in one portion. A sudden surge of heat after five minutes causes rapid boiling of the mixture. Stirring at room temperature is continued for twenty-four hours, after which the mixture is washed with water and distilled. The 1-methylcyclohexyl phenyl ketone distils at 134–140°/5 mm., n_D^{25} 1.5316; yield 42 g. (80%).

A suspension of 15.6 (0.4 mole) of sodium amide in 200 ml. of anhydrous toluene is prepared as outlined above. The toluene suspension is stirred while 42 g. (0.2 mole) of 1-methylcyclohexyl phenyl ketone is gradually added. Stirring is continued, and the mixture is heated under refluxing

conditions for six hours. After the reaction mixture is washed with water, the toluene layer is separated and distilled. 1-Methylcyclohexane-carboxamide distils at 151–154°/15 mm. and crystallizes on cooling. The amide is further purified by crystallization from pentane, m.p. 65°; yield 25 g. (88%).

A solution of 28.8 g. (0.18 mole) of bromine in 485 ml. of 20% aqueous potassium hydroxide is stirred and cooled in an ice bath while 25 g. (0.18 mole) of 1-methylcyclohexanecarboxamide is added as a fine powder. After the mixture has been stirred for an additional one-half hour, the resulting isocyanate is extracted with ether. The ethereal extract is added dropwise with stirring to 200 ml. of boiling concentrated hydrochloric acid. After the liberation of carbon dioxide ceases, the hydrochloric acid solution is concentrated in vacuum. The crystalline residue is recrystallized from a mixture of absolute ethanol and ether. A yield of 21 g. (80%) of 1-methylcyclohexylamine hydrochloride, m.p. 285° dec., is obtained.

α,α-Dimethyl-β-phenylpropionamide from Isobutyrophenone.[61] A suspension of 15.6 g. (0.4 mole) of sodium amide in 200 ml. of anhydrous toluene is prepared in a 500-ml. flask equipped with a stirrer, a dropping funnel, and a condenser protected by a drying tube. A solution of 60 g. (0.4 mole) of isobutyrophenone and 68.5 g. (0.4 mole) of benzyl bromide in 100 ml. of anhydrous toluene is added dropwise with stirring. The reaction mixture is heated on a steam bath for forty-eight hours and then is washed with water. The toluene solution is distilled. 2,2-Dimethyl-1,3-diphenylpropan-1-one is obtained in a 75% yield (71.4 g.), distilling at 142–143°/3 mm.; n_D^{20} 1.5652.

The mixture is heated and stirred for an additional hour and then cooled to room temperature, after which 21 g. (0.075 mole) of methyl iodide is added dropwise. Stirring at room temperature is continued for fifteen hours, and the benzene solution is washed with water and dried.

The dried benzene solution thus obtained is added to 6 g. (0.075 mole) of a sodium amide suspension as outlined above. The resulting sodio derivative of α-methyl-n-heptyl phenyl ketone is heated in benzene under refluxing conditions, and 37 g. (0.075 mole) of n-butyl iodide is added dropwise. This mixture is heated and stirred for an additional four hours. It is cooled, washed with water, dried, and distilled. A yield of 11 g. (55%) of α-n-butyl-α-methyl-n-heptyl phenyl ketone, b.p. 175–183°/17 mm., is obtained.

This ketone (0.04 mole) is added to a suspension of 1.6 g. (0.04 mole) of sodium amide in anhydrous benzene. The suspension is stirred and boiled for four hours and is then washed with water and distilled. A yield of 9 g. (quantitative) of α-n-butyl-α-methylcaprylamide is distilled at 167–169°/18 mm.

Without further purification, the amide so obtained is dissolved in 75 g. of concentrated sulfuric acid, and the resulting solution is cooled in a freezing mixture while an excess of a cold, saturated solution of sodium nitrite is stirred in. The mixture is warmed to about 50°, diluted with water, and extracted with ether. The ethereal extract is in turn extracted with dilute sodium hydroxide solution, and the combined alkaline extracts are acidified. The α-n-butyl-α-methylcaprylic acid distils at 160–162°/18 mm.; yield 2.4 g. (28%).

TABLE I

A. CLEAVAGE OF ALKYL, ARALKYL, OR CYCLOALKYL PHENYL KETONES
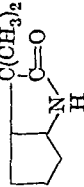
Ketone $RCOC_6H_5$ R	Product $RCONH_2$ Formula	Yield,%	References
$(CH_3)_3C-$	$C_5H_{11}NO$	Quant.	62, 32, 63
$C_2H_5C(CH_3)_2-$	$C_6H_{13}NO$	Quant.	62, 32, 15
$CH_2=CHCH_2C(CH_3)_2-$	(structure)	—	26, 27
$n\text{-}C_3H_7C(CH_3)_2-$	$C_7H_{15}NO$	Quant.	62, 32, 15
$C_2H_5C(CH_3)(C_2H_5)-$	$C_7H_{15}NO$	—	15, 32, 62
$i\text{-}C_3H_7C(CH_3)_2-$	$C_7H_{15}NO$	—	32, 64
$CH_2=CHCH_2C(CH_3)(C_2H_5)-$	(structure)	—	28
$(C_2H_5)_3C-$	$C_8H_{17}NO$	—	15, 32, 62
$n\text{-}C_3H_7C(CH_3)(C_2H_5)-$	$C_8H_{17}NO$	—	15, 32, 62
$n\text{-}C_4H_9C(CH_3)_2-$	$C_8H_{17}NO$	56	15
$C(CH_3)_2$ (cyclopentane)	(structure)	—	86

TABLE I, Part A—Continued

Ketone RCOC6H5 R	Product RCONH2 Formula	Yield, %	References
n-C7H15C(CH3)2—	C11H23NO	—	63
CH3C(C4H9-n)2—	C11H23NO	58*	15
n-C4H9C(C2H5)(C3H7-n)—	C11H23NO	83*	15
n-C5H11C(C2H5)2—	C11H23NO‡	Quant.*	15
n-C6H13C(CH3)(C2H5)—	C11H23NO†	Good	69, 72
C6H5(CH2)2C(CH3)2—	C12H17NO	—	32, 75
o-CH3C6H4CH2C(CH3)2—	C12H17NO	—	32, 75
m-CH3C6H4CH2C(CH3)2—	C12H17NO	—	32, 75
p-CH3C6H4CH2C(CH3)2—	C12H17NO	ca. 40	70, 25, 71, 72
C6H5CH2C(CH3)(C2H5)—	C12H17NO§	90, 83	70, 72, 32, 75
p-CH3OC6H4CH2C(CH3)2—	C12H17NO2	ca. 90	70
C6H5O(CH2)2C(CH3)2—	C12H17NO2	—	83
m-CH3C6H10CH2C(CH3)2—	C12H23NO	—	83
p-CH3C6H10CH2C(CH3)2—	C12H23NO	—	
C6H11(CH2)2C(CH3)2—	C12H23NO		
C6H5COC(CH3)2(CH2)4C(CH3)2—	(CH2)4 [C(CH3)2CONH2 / C(CH3)2CONH2]	78*	23, 24
n-C5H11C(C2H5)(C3H7-n)—	C12H25NO‡	—	15
n-C6H13C(C2H5)2—	C12H25NO†	—	15
n-C6H13C(CH3)(C4H9-n)—	C12H25NO	Quant.	15
n-C4H9CH(C2H5)CH2C(CH3)2—	C12H25NO	—	68
n-C8H17C(CH3)2—	C12H25NO	—	15, 65, 66

R group	Formula	Yield (%)	References
(benzo[b]thienyl)$CH_2C(CH_3)_2$—	$C_{13}H_{15}NOS$	—	80
$C_6H_5(CH_2)_3C(CH_3)_2$—	$C_{13}H_{19}NO$	—	69
$C_6H_5CH_2C(C_2H_5)_2$—	$C_{13}H_{19}NO$	ca. 40	70, 72, 73, 74
$C_6H_5CH_2C(CH_3)(C_3H_7\text{-}n)$—	$C_{13}H_{19}NO$§	—	25
$C_6H_5CH(C_2H_5)C(CH_3)_2$—	$C_{13}H_{19}NO$†§	—	77
$p\text{-}CH_3OC_6H_4(CH_2)_2C(CH_3)_2$—	$C_{13}H_{19}NO_2$	76	78
$m\text{-}CH_3C_6H_{10}(CH_2)_2C(CH_3)_2$—	$C_{13}H_{25}NO$	—	83
$C_6H_5COC(CH_3)_2(CH_2)_5C(CH_3)_2$—	$C(CH_3)_2CONH_2$—$(CH_2)_5$—$C(CH_3)_2CONH_2$	87*	23
$n\text{-}C_5H_{11}C(C_2H_5)(C_4H_9\text{-}n)$—	$C_{13}H_{27}NO$‡	—	15
$n\text{-}C_6H_{13}C(C_2H_5)(C_3H_7\text{-}n)$—	$C_{13}H_{27}NO$‡	—	15
$n\text{-}C_7H_{15}C(C_2H_5)_2$—	$C_{13}H_{27}NO$	97*	15
$n\text{-}C_9H_{19}C(CH_3)_2$—	$C_{13}H_{27}NO$	71	66
(benzo[b]thienyl)$(CH_2)_2C(CH_3)_2$—	$C_{14}H_{17}NOS$	—	80
(indanyl)$CH_2C(CH_3)_2$—	$C_{14}H_{19}NO$	—	79
$C_6H_5C(C_2H_5)(C_3H_7\text{-}n)$—	$C_{14}H_{21}NO$§	—	25, 71
$CH_2{=}C(CH_3)(CH_2)_3CH(CH_3)(CH_2)_2C(CH_3)_2$—	$C_{14}H_{27}NO$	—	66, 67
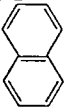
Note: References 62–96 are listed on p. 36.
* This was the yield of crude product.
† Benzamide was also isolated.
‡ The principal product was benzamide.
§ The hydrocarbon RH corresponding to the R group in the ketone was also isolated.

TABLE I, Part A—*Continued*

Ketone $RCOC_6H_5$ R	Product $RCONH_2$ Formula	Yield, %	References
$C_6H_5COC(CH_3)_2(CH_2)_6C(CH_3)_2$—	$/C(CH_3)_2CONH_2$ $(CH_2)_6$ $\backslash C(CH_3)_2CONH_2$	87	23
$n\text{-}C_6H_{13}C(C_2H_5)(C_4H_9\text{-}n)$—	$C_{14}H_{29}NO$‡	—	15
$n\text{-}C_{10}H_{21}C(CH_3)_2$—	$C_{14}H_{29}NO$	48*	30, 32, 64, 65
$\alpha\text{-}C_{10}H_7CH_2C(CH_3)_2$—	$C_{15}H_{17}NO$	—	82
$\beta\text{-}C_{10}H_7CH_2C(CH_3)_2$—	$C_{15}H_{17}NO$	—	85
$C(CH_3)(C_6H_5CH_2)$— (cyclohexyl)	$C(CH_3)CH_2CH_2C_6H_5$§ —CO— N—H	—	86
$C_6H_5CH(C_2H_5)C(C_2H_5)_2$—	$C_{15}H_{23}NO$†§	ca. 90	76, 77
$p\text{-}(CH_3)_3CC_6H_4CH_2C(CH_3)_2$—	$C_{15}H_{23}NO$	59	70, 72
$CH_2{=}CH(CH_2)_9C(CH_3)_2$—	$C_{15}H_{29}NO$	39*	66, 67
$C_6H_5COC(CH_3)_2(CH_2)_7C(CH_3)_2$—	$/C(CH_3)_2CONH_2$ $(CH_2)_7$ $\backslash C(CH_3)_2CONH_2$	—	23
$n\text{-}C_6H_{13}C(C_2H_5)(C_5H_{11}\text{-}n)$—	$C_{15}H_{31}NO$‡	Low‖	15
$n\text{-}C_7H_{15}C(C_2H_5)(C_4H_9\text{-}n)$—	$C_{15}H_{31}NO$†	—	15
$n\text{-}C_{10}H_{21}C(CH_3)(C_2H_5)$—	$C_{15}H_{31}NO$	—	65
$n\text{-}C_{11}H_{23}C(CH_3)_2$—	$C_{15}H_{31}NO$	—	65
$\alpha\text{-}C_{10}H_7CH_2C(CH_3)(C_2H_5)$—	$C_{16}H_{19}NO$	—	82
$\beta\text{-}C_{10}H_7CH_2C(CH_3)_2(C_2H_5)$—	$C_{16}H_{19}NO$	—	85

R group	Product	Yield	Ref.
$CH_2C(CH_3)_2-$ (on naphthyl–CH_3)	$C_{16}H_{19}NO$	50	85
$\alpha\text{-}C_{10}H_7(CH_2)_2C(CH_3)_2-$	$C_{16}H_{19}NO$	80	81, 82
$o\text{-}C_6H_5COC(CH_3)_2CH_2C_6H_4CH_2C(CH_3)_2-$	$o\text{-}C_6H_4\big(CH_2C(CH_3)_2CONH_2\big)_2$	—	25
$m\text{-}C_6H_5COC(CH_3)_2CH_2C_6H_4CH_2C(CH_3)_2-$	$m\text{-}C_6H_4\big(CH_2C(CH_3)_2CONH_2\big)_2$	—	25
$p\text{-}C_6H_5COC(CH_3)_2CH_2C_6H_4CH_2C(CH_3)_2-$	$p\text{-}C_6H_4\big(CH_2C(CH_3)_2CONH_2\big)_2$	—	25
$C_6H_5COC(CH_3)_2(CH_2)_8C(CH_3)_2-$	$(CH_2)_8\big(C(CH_3)_2CONH_2\big)_2$	55*	23
$n\text{-}C_8H_{17}C(C_2H_5)(C_4H_9\text{-}n)-$	$C_{16}H_{33}NO$	Low	15

Note: References 62–96 are listed on p. 36.
* This was the yield of crude product.
† Benzamide was also isolated.
‡ The principal product was benzamide.
§ The hydrocarbon RH corresponding to the R group in the ketone was also isolated.
‖ The product was isolated as the acid.
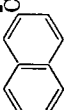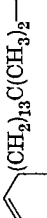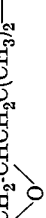
$C_6H_5COC(CH_3)_2(CH_2)_{10}C(CH_3)_2$—	$\begin{array}{c}\diagup C(CH_3)_2CONH_2\\(CH_2)_{10}\\\diagdown C(CH_3)_2CONH_2\end{array}$	86*	23
n-$C_{10}H_{21}C(C_2H_5)(C_4H_9$-$n)$—	$C_{18}H_{37}NO$‡	—	15
n-$C_{14}H_{29}C(CH_3)_2$—	$C_{18}H_{37}NO$	Quant.	68
$\begin{array}{c}CH_2C(CH_3)(C_2H_5)\text{—}\\C(CH_3)_3\end{array}$	$C_{20}H_{27}NO$	—	82
(naphthalenyl)$(CH_2)_{11}C(CH_3)_2$—	$C_{20}H_{37}NO$	Quant.	87
n-$C_{16}H_{33}C(CH_3)_2$—	$C_{20}H_{41}NO$	—	30, 68
(cyclohexenyl)$(CH_2)_{13}C(CH_3)_2$—	$C_{21}H_{39}NO$	—	68
$CH_3(CH_2)_7CH{=}CH(CH_2)_8C(CH_3)_2$—	$C_{22}H_{43}NO$	—	68
$C_6H_5COC(CH_3)_2(CH_2)_{14}C(CH_3)_2$—	$\begin{array}{c}\diagup C(CH_3)_2CONH_2\\(CH_2)_{14}\\\diagdown C(CH_3)_2CONH_2\end{array}$	—	24
n-$C_{18}H_{37}C(CH_3)_2$—	$C_{22}H_{45}NO$	—	65
n-$C_{12}H_{25}C(C_2H_5)(C_{10}H_{21}$-$n)$—	$C_{26}H_{53}NO$†	Low‖	15
$\begin{array}{c}CH_2\text{-}CHCH_2C(CH_3)_2\text{—}\\\diagdown O \diagup\end{array}$	No reaction	—	29
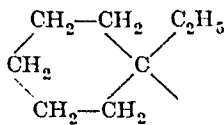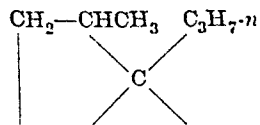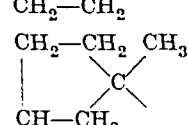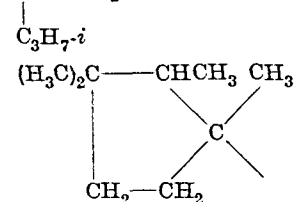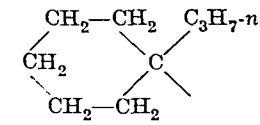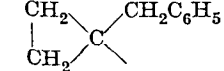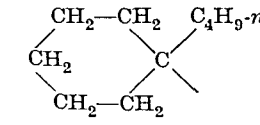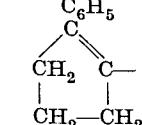
Note: References 62–96 are listed on p. 36.
* This was the yield of crude product.
† Benzamide was also isolated.
‡ The principal product was benzamide.
§ The hydrocarbon RH corresponding to the R group in the ketone was also isolated.
‖ The product was isolated as the acid.

TABLE 1 (Part B)—*Continued*

Ketone $RCOC_6H_5$ R	Product $RCONH_2$ Formula	Yield, %	Reference
CH_2—CH_2 C_2H_5 / CH_2 —C— / CH_2—CH_2	$C_9H_{17}NO$	65	19
CH_2—$CHCH_3$ C_3H_7-n / —C— / CH_2—CH_2	$C_{10}H_{19}NO$	—	18
CH_2—CH_2 CH_3 / —C— / CH—CH_2 / C_3H_7-i	$C_{10}H_{19}NO$	—	89
$(H_3C)_2C$——$CHCH_3$ CH_3 / —C— / CH_2—CH_2	$C_{10}H_{19}NO$	68	90
CH_2—CH_2 C_3H_7-n / CH_2 —C— / CH_2—CH_2	$C_{10}H_{19}NO$	65	19
CH_2 \ $CH_2C_6H_5$ / —C— / CH_2	$C_{11}H_{13}NO$	56	20, 17
CH_2—CH_2 C_4H_9-n / CH_2 —C— / CH_2—CH_2	$C_{11}H_{21}NO$	66	19
C_6H_5 \ C= / CH_2 C— / CH_2—CH_2	$C_{12}H_{13}NO$*†	—	44

Note: References 62–96 are listed on p. 36.

* Benzamide was also isolated.

† The hydrocarbon RH corresponding to the R group in the ketone was also isolated.

TABLE II

CLEAVAGE OF ALIPHATIC KETONES

Ketone RCOR'		Formula	Products	References
R	R'			
$(CH_3)_3C—$	$(CH_3)_3C—$	$C_9H_{18}O$	$(CH_3)_3CCONH_2$, $(CH_3)_3CH$	91
$(CH_3)_3C—$	$C_2H_5C(CH_3)_2—$	$C_{10}H_{20}O$	$(CH_3)_3CCONH_2$, $C_2H_5C(CH_3)_2CONH_2$ $(CH_3)_3CH$, $C_2H_5CH(CH_3)_2$	32, 91
$C_2H_5C(CH_3)_2—$	$C_2H_5C(CH_3)_2—$	$C_{11}H_{22}O$	$C_2H_5C(CH_3)_2CONH_2$, $C_2H_5CH(CH_3)_2$	32, 91
$(CH_3)_3C—$	$(C_2H_5)_3C—$	$C_{12}H_{24}O$	$(CH_3)_3CCONH_2$, $(C_2H_5)_3CCONH_2$ (ratio 5 : 1); $(CH_3)_3CH$, $(C_2H_5)_3CH$	32, 91
$(CH_3)_2CHC(CH_3)_2—$	$(CH_3)_2CHC(CH_3)_2—$	$C_{13}H_{26}O$	No reaction	32
$(CH_3)_3C—$	$C_6H_5CH_2C(CH_3)_2—$	$C_{15}H_{22}O$	$(CH_3)_3CCONH_2$, $C_6H_5CH_2CH(CH_3)_2$	32
$(CH_3)_3C—$	$C_6H_5CH_2C(C_2H_5)_2—$	$C_{17}H_{26}O$	$(CH_3)_3CCONH_2$, $C_6H_5CH_2C(C_2H_5)_2CONH_2$ (trace) $C_6H_5CH_2CH(C_2H_5)_2$	32
$C_6H_5C(CH_3)_2—$	$C_6H_5C(CH_3)_2—$	$C_{21}H_{26}O$	$C_6H_5C(CH_3)_2CONH_2$, $C_6H_5CH(CH_3)_2$	32

Note: References 62–96 are listed on p. 36.

TABLE III

CLEAVAGE OF AROMATIC KETONES

Ketone ArCOAr'		Formula	Products	References
Ar	Ar'			
C_6H_5—	2-C_4H_3S—	$C_{11}H_8OS$	$C_6H_5CONH_2$, 2-$C_4H_3SCONH_2$ (ratio 2.5 : 1 as acids)	9
C_6H_5—	3-BrC_6H_4—	$C_{13}H_9BrO$	$C_6H_5CONH_2$, 3-$BrC_6H_4CONH_2$ (ratio 5.5 : 1 as acids)	8
C_6H_5—	4-BrC_6H_4—	$C_{13}H_9BrO$	$C_6H_5CONH_2$, 4-$BrC_6H_4CONH_2$ (ratio 2.5 : 1 as acids)	8
C_6H_5—	3-ClC_6H_4—	$C_{13}H_9ClO$	$C_6H_5CONH_2$, 3-$ClC_6H_4CONH_2$ (ratio 11 : 1 as acids)	8
C_6H_5—	4-ClC_6H_4—	$C_{13}H_9ClO$	$C_6H_5CONH_2$, 4-$ClC_6H_4CONH_2$ (ratio 3.2 : 1 as acids)	8
C_6H_5—	C_6H_5—	$C_{13}H_{10}O$	$C_6H_5CONH_2$	5, 8, 36
C_6H_5—	4-CNC_6H_4—	$C_{14}H_9NO$	No cleavage*	11
C_6H_5—	4-$CH_3C_6H_4$—	$C_{14}H_{12}O$	4-$CH_3C_6H_4CONH_2$, $C_6H_5CONH_2$ (slightly more of former)	5, 36
C_6H_5—	4-$CH_3SC_6H_4$—	$C_{14}H_{12}OS$	$C_6H_5CONH_2$, 4-$CH_3SC_6H_4CONH_2$	8, 9, 11
C_6H_5—	2-$CH_3OC_6H_4$—	$C_{14}H_{12}O_2$	$C_6H_5CONH_2$ (poor yield)	11
C_6H_5—	3-$CH_3OC_6H_4$—	$C_{14}H_{12}O_2$	$C_6H_5CONH_2$, 3-$CH_3OC_6H_4CONH_2$ (ratio 3.6 : 1 as acids)	11
C_6H_5—	4-$CH_3OC_6H_4$—	$C_{14}H_{12}O_2$	4-$CH_3OC_6H_4CONH_2$, $C_6H_5CONH_2$ (ratio 2.5 : 1 as acids)	11, 5, 8, 36
C_6H_5—	2,4-$(CH_3)_2C_6H_3$—	$C_{15}H_{14}O$	2,4-$(CH_3)_2C_6H_3CONH_2$, $C_6H_5CONH_2$ (mainly the latter)	34
C_6H_5—	2,5-$(CH_3)_2C_6H_3$—	$C_{15}H_{14}O$	2,5-$(CH_3)_2C_6H_3CONH_2$, $C_6H_5CONH_2$ (mainly the latter)†	34
C_6H_5—	3,4-$(CH_3)_2C_6H_3$—	$C_{15}H_{14}O$	3,4-$(CH_3)_2C_6H_3CONH_2$, $C_6H_5CONH_2$ (equal amounts)	34

4-CH$_3$OC$_6$H$_4$—	3-CH$_3$OC$_6$H$_4$—	C$_{15}$H$_{14}$O$_3$	4-CH$_3$OC$_6$H$_4$CONH$_2$, 3-CH$_3$OC$_6$H$_4$CONH$_2$ (ratio 6.3 : 1 as acids)	11
C$_6$H$_5$—	2,4-(CH$_3$O)$_2$C$_6$H$_3$—	C$_{15}$H$_{14}$O$_3$	C$_6$H$_5$CONH$_2$ (poor yield)	11
C$_6$H$_5$—	2,5-(CH$_3$O)$_2$C$_6$H$_3$—	C$_{15}$H$_{14}$O$_3$	C$_6$H$_5$CONH$_2$ (poor yield)	11
C$_6$H$_5$—	3,4-(CH$_3$O)$_2$C$_6$H$_3$—	C$_{15}$H$_{14}$O$_3$	C$_6$H$_5$CONH$_2$, 3,4-(CH$_3$O)$_2$C$_6$H$_3$CONH$_2$ (ratio 1.2 : 1 as acids)	11
C$_6$H$_5$—	4-(CH$_3$)$_2$NC$_6$H$_4$—	C$_{15}$H$_{15}$NO	C$_6$H$_5$CONH$_2$, 4-(CH$_3$)$_2$NC$_6$H$_4$CONH$_2$	8
3-CH$_3$OC$_6$H$_4$—	3,4-(CH$_3$O)$_2$C$_6$H$_3$—	C$_{16}$H$_{16}$O$_4$	3,4-(CH$_3$O)$_2$C$_6$H$_3$CONH$_2$, 3-CH$_3$OC$_6$H$_4$CONH$_2$	11
4-CH$_3$OC$_6$H$_4$—	3,4-(CH$_3$O)$_2$C$_6$H$_3$—	C$_{16}$H$_{16}$O$_4$	3,4-(CH$_3$O)$_2$C$_6$H$_3$CONH$_2$, 4-CH$_3$OC$_6$H$_4$CONH$_2$	11
C$_6$H$_5$—	1-C$_{10}$H$_7$—	C$_{17}$H$_{12}$O	C$_6$H$_5$CONH$_2$, C$_{10}$H$_8$ (trace)	34
C$_6$H$_5$—	2-C$_{10}$H$_7$—	C$_{17}$H$_{12}$O	2-C$_{10}$H$_7$CONH$_2$, C$_6$H$_5$CONH$_2$ (ratio 6 : 1); (ratio 2 : 1 as acids)	9, 34
4-ClC$_6$H$_4$—	4-C$_6$H$_5$C$_6$H$_4$—	C$_{19}$H$_{13}$ClO	4-C$_6$H$_5$C$_6$H$_4$CONH$_2$, 4-ClC$_6$H$_4$CONH$_2$ (ratio 2.3 : 1 as acids)	33
C$_6$H$_5$—	4-C$_6$H$_5$C$_6$H$_4$—	C$_{19}$H$_{14}$O	C$_6$H$_5$CONH$_2$, 4-C$_6$H$_5$C$_6$H$_4$CONH$_2$ (ratio 3 : 1 as acids)	9, 33
4-CH$_3$C$_6$H$_4$—	4-C$_6$H$_5$C$_6$H$_4$—	C$_{20}$H$_{16}$O	4-C$_6$H$_5$C$_6$H$_4$CONH$_2$, 4-CH$_3$C$_6$H$_4$CONH$_2$ (ratio 1.08 : 1 as acids)	33
4-CH$_3$OC$_6$H$_4$—	4-C$_6$H$_5$C$_6$H$_4$—	C$_{20}$H$_{16}$O$_2$	4-C$_6$H$_5$C$_6$H$_4$CONH$_2$, 4-CH$_3$OC$_6$H$_4$CONH$_2$ (ratio 1.45 : 1 as acids)	33
1-C$_{10}$H$_7$—	4-C$_6$H$_5$C$_6$H$_4$—	C$_{23}$H$_{16}$O	4-C$_6$H$_5$C$_6$H$_4$CONH$_2$, C$_{10}$H$_8$ (10% of mixture)	33
2-C$_{10}$H$_7$—	4-C$_6$H$_5$C$_6$H$_4$—	C$_{23}$H$_{16}$O	4-C$_6$H$_5$C$_6$H$_4$CONH$_2$, 2-C$_{10}$H$_7$CONH$_2$ (ratio 1.24 : 1 as acids)	33
C$_6$H$_5$—	(C$_6$H$_5$)$_3$C—	C$_{26}$H$_{20}$O	No reaction	8

Note: References 62–96 are listed on p. 36.

* In this experiment the cyano group was hydrolyzed and the product was p-C$_6$H$_5$COC$_6$H$_4$CO$_2$H

† Catalytic quantities of mercury were added in a second experiment; 2,5-dimethylbenzamide and benzamide were obtained in a ratio of 1 : 3.5.

TABLE IV

Cleavage of Alicyclic Ketones

Ketone	Products	Formula	References
(cyclopentanone, with (CH₃)₂, CH₂, =O)	(cyclopentane) i-H₇C₃—CONH₂	$C_9H_{17}NO$	92
(cyclopentanone with (CH₃)₂, CH₃, =O)	$(CH_3)_2CH(CH_2)_2C(CH_3)_2CONH_2$	$C_9H_{19}NO$	39
(cyclopentanone with (CH₃)₂, CH₂, CH₃, =O)	(cyclopentane) i-H₇C₃, CH₃, CONH₂	$C_{10}H_{19}NO$	4
(cyclopentanone with (CH₃)₂, CH₃, =O)	$(CH_3)_2CHCH(CH_3)CH_2C(CH_3)_2CONH_2$ and $(CH_3)_2CHCH_2CH(CH_3)C(CH_3)_2CONH_2$	$C_{10}H_{21}NO$	96
(bicyclic ketone with (CH₃)₂, =O)	$C_6H_5CH_2C(CH_3)_2CONH_2$	$C_{11}H_{15}NO$	73, 74, 88

TABLE IV (*Continued*)

CLEAVAGE OF ALICYCLIC KETONES

Ketone	Products	Formula	Reference
O=, (C₃H₇)₂, CH₃, C₃H₇, CH₃	C₃H₇CH(CH₃)CH₂CH(CH₃)C(C₃H₇)₂CONH₂, and (C₃H₇)₂CHCH(CH₃)CH₂C(CH₃)(C₃H₇)CONH₂	C₁₆H₃₃NO	93
C₂H₅, CH₂C₆H₅, ...O, CH₃	structure with CH₃, CONH₂, (CH₃)₂, C₆H₅CH₂(C₂H₅)HC	C₁₉H₂₉NO	38
O=, CH₃, CH₂C₆H₅, CH₃, CH₃, C₆H₅CH₂	C₆H₅CH(CH₃)CH₂CH(CH₃)C(CH₃)(CH₂C₆H₅)CONH₂ and C₆H₅CH(CH₃)CH(CH₃)CH₂C(CH₃)(CH₂C₆H₅)CONH₂	C₂₁H₂₅NO	93
(CH₂C₆H₅)₂, O=, CH₃	structure with CH₃, CONH₂, (CH₃)₂, (C₆H₅CH₂)₂HC	C₂₁H₃₁NO	38
(CH₃)₂, O=	No reaction		92

REFERENCES

[62] Haller and Bauer, *Compt. rend.*, **148**, 127 (1909).

[63] Grünfeld, *Ann. chim. Paris*, [10] **20**, 304 (1933).

[64] Haller and Bauer, *Compt. rend.*, **149**, 5 (1909).

[65] Mentzer, Buu-Hoï, and Cagniant, *Bull. soc. chim. France*, [5] **10**, 141 (1943).

[66] Buu-Hoï and Cagniant, *Rec. trav. chim.*, **65**, 246 (1946).

[67] Laboratoires français de chimiothérapie, Brit. pat. 617,892 (1949) [*C. A.*, **43**, 7037 (1949)].

[68] Buu-Hoï and Cagniant, *Z. physiol. Chem.*, **279**, 76 (1943).

[69] Ramart and Hoch, *Bull. soc. chim. France*, [5] **5**, 848 (1938).

[70] Mentzer, Buu-Hoï, and Cagniant, *Bull. soc. chim. France*, [5] **9**, 813 (1942).

[71] Haller and Dumesnil, *Compt. rend.*, **153**, 111 (1911).

[72] Laboratoires français de chimiothérapie, Brit. pat. 613,111 [*C. A.*, **43**, 5800 (1949)].

[73] Haller and Bauer, *Compt. rend.*, **150**, 1472 (1910).

[74] Haller and Bauer, *Ann. chim. Paris*, [9] **16**, 340 (1921).

[75] Haller and Bauer, *Compt. rend.*, **153**, 21 (1911).

[76] Ramart, Albesco, and Haller, *Compt. rend.*, **174**, 1289 (1922).

[77] Albesco, *Ann. chim. Paris*, [9] **18**, 216 (1922).

[78] Buu-Hoï and Cagniant, *Compt. rend.*, **219**, 455 (1944).

[79] Cagniant, *Compt. rend.*, **226**, 675 (1948).

[80] Cagniant, *Bull. soc. chim. France*, 1949, 382 (5-6).

[81] Laboratoires français de chimiothérapie, Swiss pat. 236,798 (1945).

[82] Cagniant, Mentzer, and Buu-Hoï, *Bull. soc. chim. France*, [5] **10**, 146 (1943).

[83] Mentzer and Chopin, *Bull. soc. chim. France*, [5] **15**, 586 (1948).

[84] Mentzer, Buu-Hoï, and Cagniant, Swiss pat. 237,870 (1945).

[85] Cagniant and Buu-Hoï, *Bull. soc. chim. France*, [5] **10**, 349 (1943).

[86] Buu-Hoï and Cagniant, *Compt. rend.*, **217**, 26 (1943).

[87] Buu-Hoï and Cagniant, *Bull. soc. chim. France*, [5] **9**, 355 (1942).

[88] Rothstein and Saville, *J. Chem. Soc.*, 1949, 1946.

[89] Bouveault and Levallois, *Bull. soc. chim. France*, [4] **3**, 968 (1910).

[90] Shive, Horeczy, and Lochte, *J. Am. Chem. Soc.*, **62**, 2744 (1940).

[91] Haller and Bauer, *Compt. rend.*, **150**, 664 (1910).

[92] Ramotkin and Kagan, *J. Gen. Chem. U.S.S.R.*, **16**, 885 (1946) [*C. A.*, **41**, 2019 (1947)].

[93] Haller and Cornubert, *Compt. rend.*, **158**, 1739 (1914).

[94] Haller and Ramart-Lucas, *Compt. rend.*, **173**, 682 (1921).

[95] Haller and Bauer, *Ann. chim. Paris*, [9] **8**, 117 (1917).

[96] Haller and Cornubert, *Compt. rend.*, **158**, 1616 (1914).

CHAPTER 2

THE GATTERMANN SYNTHESIS OF ALDEHYDES

WILLIAM E. TRUCE

Purdue University

CONTENTS

INTRODUCTION

Gattermann developed two methods for introducing the aldehyde group into aromatic compounds. The first of these, known as the Gattermann-Koch reaction,[1] uses a mixture of carbon monoxide and hydrogen chloride in the presence of a mixture of anhydrous aluminum chloride and cuprous chloride. It is not adaptable to the preparation of aldehydes

$$\text{ArH} + \text{CO} + \text{HCl} \xrightarrow[\text{Cu}_2\text{Cl}_2]{\text{AlCl}_3} \text{ArCHO} + \text{HCl}$$
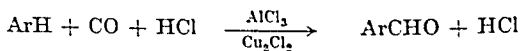
from phenols or phenolic ethers, however. The second method employs a mixture of hydrogen cyanide and hydrogen chloride with or without a catalyst, and permits the introduction of an aldehyde group into phenols, naphthols, and their ethers, and, under special conditions, into aromatic hydrocarbons and related compounds.[2] This chapter is concerned with the second method.

$$\text{ArH} + \text{HCN} + \text{HCl} \xrightarrow[\text{(2) H}_2\text{O}]{\text{(1) AlCl}_3 \text{ or ZnCl}_2} \text{ArCHO} + \text{NH}_4\text{Cl}$$
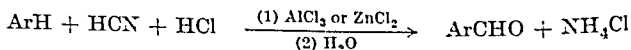
Aluminum chloride must be used as a catalyst with certain phenols and phenolic ethers;[3] with others, zinc chloride may replace aluminum chloride.[4] A modification of this method, which was described by Adams and his co-workers,[5,6] employs zinc cyanide as both a convenient source of anhydrous hydrogen cyanide and as a catalyst. When hydrogen chloride is introduced into the reaction mixture, hydrogen cyanide and zinc chloride are formed *in situ*. In those reactions that require anhydrous aluminum chloride as a catalyst, it may be introduced with the zinc cyanide.[6] Polyhydric phenols such as resorcinol and phloroglucinol in which the hydroxyl groups are *meta* to each other do not require a catalyst.[3]

More vigorous conditions are required to introduce the aldehyde group into aromatic hydrocarbons; e.g., the temperature must be raised.[7,8]

[1] Crounse, *Organic Reactions*, 5, 290, John Wiley & Sons, 1949.
[2] Gattermann, *Ber.*, 31, 1149 (1898).
[3] Gattermann, *Ann.*, 357, 313 (1907).
[4] Gattermann and von Horlacher, *Ber.*, 32, 284 (1899).
[5] Adams and Levine, *J. Am. Chem. Soc.*, 45, 2373 (1923).
[6] Adams and Montgomery, *J. Am. Chem. Soc.*, 46, 1518 (1924).
[7] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, 1936, 339.
[8] Hinkel, Ayling, and Morgan, *J. Chem. Soc.*, 1932, 2793.

The choice of solvent and the proportion of aluminum chloride and hydrogen cyanide relative to the amount of hydrocarbon present affect the yields obtained. Zinc cyanide or sodium cyanide may be used in place of hydrogen cyanide.[8,9]

MECHANISM

The mechanism of the reaction appears to be complex and has not been fully elucidated. Hinkel and his co-workers have presented evidence indicating that the mechanism may vary with the nature of the compound into which the aldehyde group is being introduced and with the conditions of reaction.[8,10-14] A study has been made of the products of the reaction of hydrogen cyanide, hydrogen chloride, and aluminum chloride with each other in the absence of an aromatic nucleus in order to find one or more species which might be serving as the agent of aromatic substitution. Thus, hydrogen cyanide reacts with aluminum chloride to give a complex with the structure I,[13] and with hydrogen chloride to give the "sesquichloride" II.[15,16] In turn, II gives chloromethyleneformamidine (III) when heated to 100°,[12] and iminoformylcarbylamine (IV) when heated with quinoline.[17] Aluminum chloride complexes of these latter substances

$$AlCl_3 \cdot HN{=}CHNC$$
I

$$NH{=}CHNHCHCl_2 \cdot HCl$$
II

$$ClCH{=}NCH{=}NH$$
III
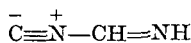
$$\overset{-}{C}{\equiv}\overset{+}{N}{-}CH{=}NH$$
IV

were also prepared.[10,12,13] Since modern spectral methods were unavailable at the time this work was carried out, and in view of the experimental difficulties involved in characterizing such compounds, further investigation is desirable before the structures assigned can be considered as definitely established.

Although one or more of the substances mentioned or ions derived from them may serve as intermediates in the Gattermann reaction, it should be noted that yields of aldehydes in excess of 50% based on the hydrogen cyanide employed are often obtained. It follows then that, if an intermediate such as I, II, III, or IV is effective as the aromatic substituting

[9] Niedzielski and Nord, *J. Am. Chem. Soc.*, **63**, 1462 (1941).
[10] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1935**, 674.
[11] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1936**, 184.
[12] Hinkel and Dunn, *J. Chem. Soc.*, **1930**, 1834.
[13] Hinkel and Dunn, *J. Chem. Soc.*, **1931**, 3343.
[14] Hinkel and Watkins, *J. Chem. Soc.*, **1944**, 647.
[15] Dains, *Ber.*, **35**, 2496 (1902).
[16] Gattermann and Schnitzspahn, *Ber.*, **31**, 1770 (1898).
[17] Neff, *Ann.*, **287**, 337 (1895).

reagent in these reactions, it must be able to utilize both its carbon atoms for the formation of aldehyde.

In any event the reaction apparently proceeds by the formation of the conjugate acid of hydrogen cyanide (V) or of one of a number of other possible ions, which, with the aid of aluminum chloride, can serve as a

$$HC\equiv NH^+ \qquad ArCH=NH_2^+ \qquad ArCH=NH \cdot AlCl_3$$
$$V \qquad\qquad VI \qquad\qquad\qquad VII$$
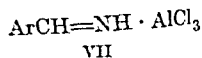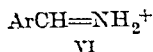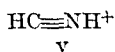
substituting agent in a reaction which is presumably analogous to Friedel-Crafts acylation. Certain reactions, however, proceed without the aid of aluminum chloride or other catalyst. Apparently the product from the Gattermann reaction is the conjugate acid VI or aluminum chloride complex VII of the aldimine or a more complex derivative of it. Generally the nitrogen-containing substance is not isolated but is hydrolyzed directly to the aldehyde.

A detailed discussion of the mechanisms must await a thorough study of the kinetics of the reactions.

SCOPE AND LIMITATIONS

Ethers of Monohydric Phenols

A methylene formamidine adduct is formed by treating a mixture of a phenol ether, anhydrous aluminum chloride, and anhydrous hydrogen cyanide with anhydrous hydrogen chloride at approximately 40°.[2] This adduct is readily hydrolyzed to the corresponding aldehyde. The following list illustrates those phenol ethers into which the aldehyde group has been introduced in yields of 80 to 100%:[2,3,8] anisole, phenetole, o- and m-chloroanisole, m-chlorophenetole, the methyl and ethyl ethers of o- and m-cresol, and the methyl ether of 1-naphthol. The aldehyde group enters the position para to the ether linkage unless the para position is occupied, when it enters the position ortho to the alkoxyl group. For example, p-cresyl methyl ether yields 2-methoxy-5-methylbenzaldehyde (80%).[2,3] However, the preference of para substitution to ortho or occasional meta substitution is very strong both in the reactions with phenols and in the reactions with phenol ethers. The introduction of an aldehyde group into 2,4,6-trimethylanisole results in the formation of 3-hydroxy-2,4,6-trimethylbenzaldehyde (VIII) in only 5–10% yield along with small amounts of an unidentified hydroxydimethylbenzaldehyde.[18] Demethylation of the ether takes place concomitantly with the introduction of the aldehyde group. Other examples of demethylation of methyl ethers are given in the tables.

[18] von Auwers and Mauss, Ber., 61, 1495 (1928).

With certain activated nuclei, hydrogen cyanide and hydrogen chloride may be used without a catalyst as in the preparation of the dialdehyde IX from the trimethylene ether of β-naphthol.[3]   Occasionally, zinc chloride
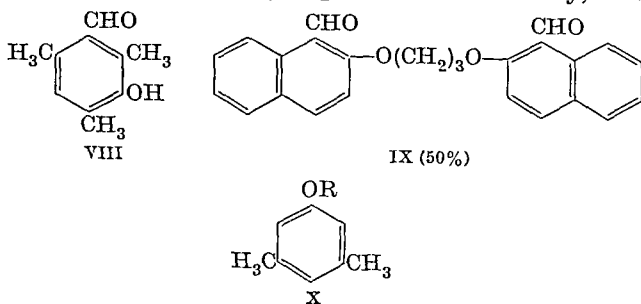
may be used to replace aluminum chloride advantageously, for example, with the methyl and ethyl ethers of 3,5-dimethylphenol (X).[3]   However, with few exceptions, aldehydes of monohydric phenol ethers can be prepared only with the use of aluminum chloride as a catalyst.

Attempts have been made to avoid the direct use of anhydrous hydrogen cyanide because of the hazard involved therein.   Adams and his coworkers supplied a method whereby the phenol ether is treated in dry benzene with 2 equivalents of zinc cyanide.[5,6]   After dry hydrogen chloride is passed through the solution to its saturation point, $1\frac{1}{2}$ equivalents of anhydrous aluminum chloride are added and dry hydrogen chloride is again introduced at a temperature of approximately 40–45°.   By the above procedure, excellent yields of anisaldehyde, 2-methoxy-5-methyl-benzaldehyde, and 2-methoxy-1-naphthaldehyde have been reported; diphenyl ether gave p-phenoxybenzaldehyde in 50% yield.

Replacement of zinc cyanide by sodium or potassium cyanide or replacement of benzene by other solvents generally reduces the yields of aldehydes.[6,9]   Zirconium cyanide in the presence of zirconium chloride in dry benzene gave only a poor yield of anisaldehyde from anisole under the conditions used.[18a]

Monohydric Phenols

The procedure just described for introducing an aldehyde group into a phenol ether must usually be modified when introducing an aldehyde group into a monohydric phenol.[3]   The phenol is treated with hydrogen cyanide in benzene, and the mixture is cooled with a salt-ice bath.   Powdered aluminum chloride is slowly added, and the temperature is brought to 40° while anhydrous hydrogen chloride is introduced.   The yields appear to vary with the structure of the phenol:[3,19]   phenol (30%),

[18a] Krishnamurti, *J. Madras Univ.*, (1928) [*C. A.*, **23**, 2161 (1929)].

[19] Gattermann and Berchelmann, *Ber.*, **31**, 1765 (1898).

o-cresol (35–40%), m-cresol (45–50%), 2,3-dimethylphenol (60%), 2,5-dimethylphenol (80%), 3,5-dimethylphenol (quantitative), carvacrol (30%), m-chlorophenol (50%), m-bromophenol (10%), p-cresol (5%). Only one aldehyde group is introduced, and it always enters *para* to the hydroxyl group if that position is unoccupied. If the *para* position is blocked, the reaction may not proceed at all or it may lead in poor yield to a product in which the aldehyde group is *ortho* to the hydroxyl group. 2-Naphthol is an exception in that an excellent yield of 2-hydroxy-1-naphthaldehyde is obtained.[3] 2,3-Dimethylphenol yields 4-hydroxy-2,3-dimethylbenzaldehyde (XI) in 60% yield with only a trace of the compound in which the aldehyde group has entered *ortho* to the hydroxyl group.[3,18] 2,3,4-Trimethylphenol (XII), however, also yields 4-hydroxy-2,3-dimethylbenzaldehyde (XI) as the chief product with only a trace of 2-hydroxy-3,4,5-trimethylbenzaldehyde (XIII), showing that the driving force towards *para* substitution is so strong that replacement of an alkyl group by an aldehyde group is preferred to *ortho* substitution. Several other examples of ring dealkylation are given in the tables.
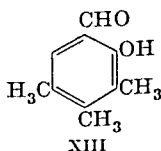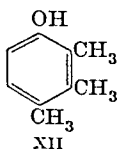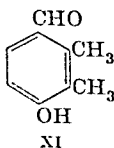
Zinc chloride or the Adams modification may be substituted for aluminum chloride in the reactions with monohydric 2-naphthols that are unsubstituted in the 1-position and with 1-naphthols that are unsubstituted in the 4-position; the products containing the aldehyde group in the 1- and 4-position, respectively, are formed in almost quantitative yields.[3,4] In general, however, monohydric phenols fail to react unless aluminum chloride is added as a catalyst.[6] Using the Adams modification with aluminum chloride, the following phenolic aldehydes were prepared: 4-hydroxy-3-methylbenzaldehyde (38%),[6] 4-hydroxy-5-isopropyl-2-methylbenzaldehyde (quantitative),[6,20,21] p-carvacrolaldehyde (good),[20,21] and 4-hydroxy-2-methylbenzaldehyde (30%).[22]

This explanation is supported by the fact that neither gallacetophenone (XIV) nor isopaeonol (XV) yields a γ-substitution product when treated with zinc cyanide, hydrogen chloride, and aluminum chloride.[32,35]   When
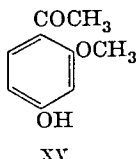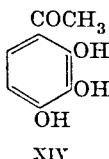
γ substitution does occur yields are frequently excellent, e.g., 3-acetyl-2-hydroxy-4,6-dimethoxybenzaldehyde (84%),[28] 3,5-dicarbethoxy-2,4,6-trihydroxybenzaldehyde (85%),[28] 2,6-dihydroxy-3-propionylbenzaldehyde (64%),[33] 3-carbomethoxy-2,6-dihydroxybenzaldehyde (65%),[29] 3-carbalkoxy-2,6-dihydroxy-4-methylbenzaldehydes (quantitative).[31]

The Adams modification using zinc cyanide and hydrogen chloride in the absence of aluminum chloride has also been successful in the preparation of aldehydes of polyhydric phenols having no nuclear deactivating substituents.[5,36-40]   Representative compounds prepared by this procedure follow: β-resorcylaldehyde (95%),[5] 2,4-dihydroxy-6-methylbenzaldehyde (85%),[5] 3-ethyl-2,4-dihydroxybenzaldehyde (74-80%),[37] and 2,4-dihydroxy-3-methoxybenzaldehyde (93%).[37] The formation of dialdehydes in low yields has been observed with phloroglucinol and its alkyl-substituted derivatives;[38] phloroglucinol-3,5-dicarboxaldehyde is isolated from phloroglucinol in 1.5% yield. The yield of dialdehyde is increased to 6.6% with methylphloroglucinol and to 24% with ethylphloroglucinol.

Zinc chloride has been successfully substituted for aluminum chloride in a number of instances.[3,23,41,42] Its use with dihydric naphthols has been shown to result in the entrance of the aldehyde group into a free 1- or 4-position in the molecule in preference to a free 2-position.[23] Thus, 1,8-dihydroxynaphthalene when treated with hydrogen cyanide, hydrogen chloride, and zinc chloride gives 4,5-dihydroxy-1-naphthaldehyde (24%) with only a very small amount of 1,8-dihydroxy-2-naphthaldehyde (0.8%). On the other hand, substitution in the 2-position is apparently favored

Monoalkyl Ethers of Dihydric Phenols

In the monoalkyl ethers of resorcinol the aldehyde group usually enters *para* to the hydroxyl group rather than *para* to the alkoxyl group. For example, employment of Gattermann's procedure with aluminum chloride on the monomethyl ether of resorcinol results in a 75–80% yield of 4-hydroxy-2-methoxy-benzaldehyde.[3,19] In several instances, zinc chloride has been substituted for aluminum chloride, as in the preparation of 6-hydroxy-3-methyl-2,3-dihydrobenzofuran-5-carboxaldehyde.[51] In this latter synthesis, the position *para* to the hydroxyl group is occupied and substitution occurs in the position *para* to the ether linkage.

Polyalkoxy Derivatives of Benzene

The Gattermann procedure with aluminum chloride is effective for the introduction of the aldehyde group into polyalkoxybenzenes.[2,3,52] As with polyhydric phenols, the aldehyde group always enters *para* to an alkoxyl group if this position is available; resorcinol dimethyl ether is converted to 2,4-dimethoxybenzaldehyde in 80% yield by the Adams modification with added aluminum chloride.[6] Substitution may occur *ortho* to the alkoxyl group when the *para* position is blocked; e.g., the dimethyl and diethyl ethers of hydroquinone are reported to give 2,5-dialkoxybenzaldehydes in unspecified yields.[3]

When mixed ethers are subjected to the Gattermann reaction, a mixture of the possible isomeric aldehydes is formed.[53,54] Determination of the relative amounts of each has demonstrated the following order of influence by the alkoxyl group in directing the aldehyde group to the *para* position:[53]

$$CH_2=CHCH_2O— > C_2H_5O— > CH_3CH_2CH_2O—, \; CH_3O—$$
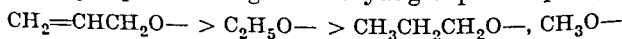
Molecules with Two Non-Fused Aromatic Nuclei

With molecules having two aromatic nuclei, each of which contains an ether linkage, it is possible to introduce an aldehyde group into each ring. The reaction has been applied to dimethylene and trimethylene ethers of phenol, o-cresol, m-cresol, 2,5-dimethylphenol, and 1- and 2-naphthol. The yields of dialdehydes vary from 30% to 75%.[3]
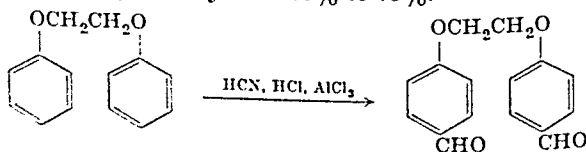
[51] Karrer, Glattfelder, and Widmer, *Helv. Chim. Acta*, 3, 548 (1920).
[52] Gattermann and Eggers, *Ber.*, 32, 289 (1899).
[53] Sonn and Patschke, *Ber.*, 58, 1698 (1925).
[54] Unzmade and Orwoll, *J. Am. Chem. Soc.*, 65, 1736 (1943).

Similarly, 2,2′-dimethoxy- and 2,2′-diethoxy-biphenyl react to give the 5,5′-dialdehydes.[3]   The corresponding 2,2′-dihydroxybiphenyl, however, is converted to dibenzofuran by the aluminum chloride, and only one aldehyde group is introduced.[55]
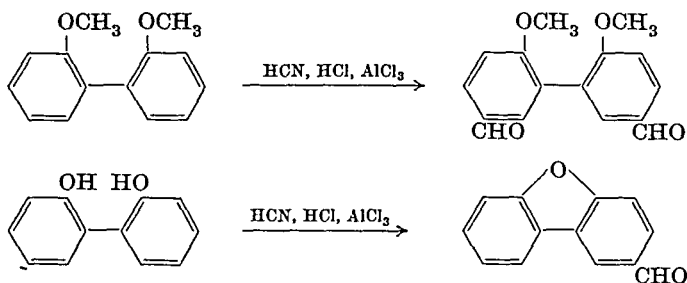
Aromatic Hydrocarbons

Gattermann was unable to introduce the aldehyde group into aromatic hydrocarbons under the conditions he used.   Tetralin was an exception, since it formed 3,4-tetramethylenebenzaldehyde in 33% yield.   In fact, Gattermann often used benzene and other hydrocarbons as solvents in his reactions.   It was later discovered, however, that an aldehyde group could be introduced into benzene provided that the conditions were modified so that free aluminum chloride was present.[8]   At 40°, in benzene, the complex of aluminum chloride with chloromethylene formamidine is not dissociated and reaction does not occur.   If the temperature is raised to 80° or above, the complex appears to dissociate to some extent, yielding free aluminum chloride, and reaction does occur.   If excess aluminum chloride is added, the yield of benzaldehyde is increased from 14% to 75%.[8]   It is advantageous to employ a mole-per-mole ratio of aluminum chloride to hydrogen cyanide when the aromatic compound is not very susceptible to polymerization;   otherwise, the amount of aluminum chloride must be reduced and the time of reaction increased.   The yields of aldehydes reported by Hinkel and his co-workers are based on the amount of hydrogen cyanide used instead of on the amount of aromatic compound as reported by Gattermann.   On the assumption that 2 moles of hydrogen cyanide are required for every mole of aromatic compound converted to the aldehyde, the yields (which formerly were calculated to be only 50% based on the aromatic compound) actually correspond to yields of nearly 100% when a 1 : 1 molar ratio of reactants was employed. It is certain, however, that 2 moles of hydrogen cyanide are not necessary for introduction of an aldehyde group into phenols and phenol ethers under all conditions.

[55] Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1937**, 778.

Just as the yield of benzaldehyde is markedly increased as the temperature is raised from that of the room to 100°,[7] so the yield of aldehydes from other aromatic hydrocarbons is also increased. Unfortunately, the increase in temperature also increases the tendency for aluminum chloride to induce polymerization of the hydrocarbon. Hinkel and his co-workers recommend approximately 70° as the optimum temperature for most reactions.[7]

Aldehydes can be prepared from liquid aromatic hydrocarbons by using excess hydrocarbon as the solvent; but, when the hydrocarbons are not liquid, are not easily procurable, or are unstable in the presence of aluminum chloride, the reaction must be modified by employment of inert solvents. Tetrachloroethane, o-dichlorobenzene, and chlorobenzene are suitable reaction media since they are good solvents for the hydrocarbons, hydrogen cyanide, and the final products, and since their high boiling points permit their use over a wide temperature range.[7] Tetrachloroethane appears to promote the aldehyde synthesis, but it also increases the tendency of the aluminum chloride to cause polymerization of the hydrocarbons. Indene is so readily polymerized that introduction of the aldehyde group has not been achieved.

Polymerization can usually be reduced by employing a solvent with a lower chlorine content and by using but a slight excess of aluminum chloride, with a subsequent increase in the time of reaction. The effect of solvent is quite pronounced with biphenyl, which yields a monoaldehyde in chlorobenzene or o-dichlorobenzene, and a dialdehyde when the solvent medium is tetrachloroethane. Pertinent to the mechanism of the latter reaction is the fact that the monoaldehyde cannot be converted to the dialdehyde under the same conditions.[7] A solvent effect has also been observed in the preparation of tolualdehydes from toluene; with excess toluene as solvent both m- and p-tolualdehyde are obtained, but with chlorobenzene as solvent only p-tolualdehyde is obtained.[56]

A few of the aldehydes formed in good yields from the representative hydrocarbons as described by Hinkel and his co-workers are: benzaldehyde (75%), p-tolualdehyde (91%), 3,4-dimethylbenzaldehyde (85%), 2,4,6-trimethylbenzaldehyde (67–83%), 4-phenylbenzaldehyde (75%), fluorene-2-carboxaldehyde (76%), and acenaphthene-5-carboxaldehyde (70–90%).[7,8,10,57]

The Adams modification of the Gattermann reaction using zinc cyanide in the presence of aluminum chloride was employed by Fuson and his co-workers for the preparation of some polyalkylated benzaldehydes.[58,59]

[56] Niedzielski and Nord, J. Org. Chem., 8, 147 (1943).

[57] Hinkel, Brit. pat. 397,124 (1933) [C. A., 28, 778 (1934)].

[58] Fuson, Horning, Rowland, and Ward, Org. Syntheses, Coll. Vol. III, 549 (1955).

[59] Fuson, Horning, Ward, Rowland, and Marsh, J. Am. Chem. Soc., 64, 31 (1942).

Using tetrachloroethane as the solvent and a reaction temperature of 70°, 1,3,5-trialkylbenzenes are converted to 2,4,6-trialkylbenzaldehydes in 38–83% yield.

Complications that may be encountered with aromatic hydrocarbons are alkylation and alkyl migration; from ethylbenzene both mono- and di-ethylbenzaldehyde can be isolated.[56]

Sodium cyanide and hydrogen chloride with aluminum chloride have also been used.[9,56,60] This combination is generally applicable to aromatic hydrocarbons other than benzene. Aluminum chloride in excess of that required to form a 1 : 1 complex with chloromethyleneformamidine is necessary.[9] The yields of the corresponding aldehydes obtained from toluene and the isomeric xylenes appear to coincide with the polarity of the hydrocarbon reactants. Under these conditions, extensive migration and alkylation are observed so that some 2,4-dimethylbenzaldehyde is obtained from all three xylenes. The yields of this compound, however, vary with the xylene used: from o-xylene 75%, from m-xylene 26%, and from p-xylene 17%. In the reaction mixtures from m-xylene and p-xylene, 2,4,5-trimethylbenzaldehyde may be isolated in 13% and 21% yield, respectively; no trimethylbenzaldehyde is obtained from o-xylene.[56]

Aromatic Amines

The Gattermann reaction generally cannot be applied to aromatic amines. The preparation of p-aminobenzaldehyde by the reaction of hydrogen cyanide and hydrogen chloride on aniline in ether solution has been reported but not confirmed.[61] Hinkel and his co-workers have obtained merely complex condensation products instead of aldehydes from aniline, dimethylaniline, and diphenylamine.[55]

Pyrroles and Indoles

The aldehyde group is introduced with great ease into certain pyrroles and indoles. This reaction proceeds so readily that frequently no catalyst is required.[62–65] Both diethyl ether and chloroform have been employed as solvents. The yields often vary with the solvent and have been considerably better in chloroform than in ether.[63] An outstanding example

[60] Mistritta and Nord, *Nature*, 145, 387 (1940).
[61] Wu, *J. Am. Chem. Soc.*, 66, 1421 (1944).
[62] Fischer and Ammann, *Ber.*, 56, 2319 (1923).
[63] Fischer and Zerweck, *Ber.*, 56, 519 (1923).
[64] Reichstein, *Helv. Chim. Acta*, 13, 349 (1930).
[65] Soka, *Ber.*, 56, 2058 (1923).

is 2,3,5-trimethylpyrrole, which is converted in 67% yield to 2,4,5-trimethylpyrrole-3-carboxaldehyde in chloroform solution but which apparently gives no product in diethyl ether.

Aldehyde groups have not been introduced into unsubstituted pyrrole or indole.[61,66] This failure has been explained as the result of the reaction of the intermediate aldimine hydrochloride with the pyrrole or indole to give complex, colored condensation products.[66] No difficulty is encountered in introducing the aldehyde group into 1-alkylpyrroles such as 1-methylpyrrole, 1-n-butylpyrrole, 1-i-amylpyrrole, and 1-furfurylpyrrole.[66] The aldehyde group enters the 2- or 5-position if one is free, but if both these positions are occupied, it may readily enter the 3- or 4-position. Another noteworthy fact is that the carbethoxy group and various acyl groups apparently do not prevent the reaction; many of the best yields of pyrrole aldehydes have been from pyrroles containing such substituents which are normally nuclear deactivating. In the absence of an open position, a carbethoxy group may be replaced by an aldehyde group.[67] The aldehydes from a selected list of pyrroles are given below with the yields obtained.

).
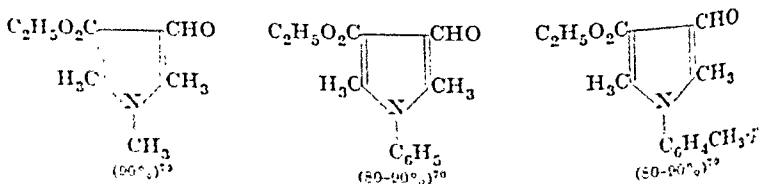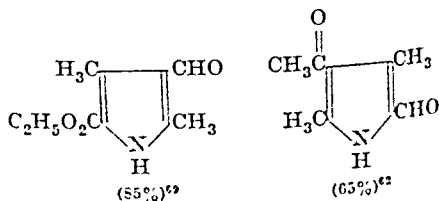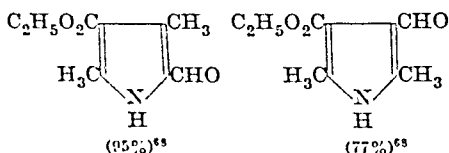
Thiophenes and Thiazoles

Few applications of the Gattermann reaction in the thiophene series have been made. Thiophene is less reactive than furan and pyrrole, and the aldehyde group may be introduced (in poor yield) only in the presence of aluminum chloride.[64] Undoubtedly, the tendency of thiophene to polymerize under acidic conditions is the chief obstacle to the application of the Gattermann reaction in this series.

2-Hydroxy-4-methylthiazole-5-carboxaldehyde (25%) is prepared by the use of hydrogen cyanide and hydrogen chloride in the absence of a catalyst, but 4-methylthiazole fails to react.[76]

Enols

Ethyl acetoacetate dissolved in benzene is converted by hydrogen cyanide and hydrogen chloride in the presence of aluminum chloride into ethyl α-formiminoacetoacetate hydrochloride.[77]

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow[C_6H_6]{HCN, HCl, AlCl_3,} CH_3COCHCO_2C_2H_5$$
$$\underset{CH=NH \cdot HCl}{|}$$
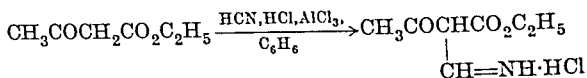
Analogous results are obtained with acetylacetone, and, presumably, other active methylene compounds would act similarly. Simple olefins, however, do not yield the corresponding aldehydes under the conditions of the Gattermann reaction.[78]

ALTERNATIVE METHODS FOR DIRECT INTRODUCTION OF AN ALDEHYDE GROUP

Several alternative methods for the direct introduction of aldehyde groups into aromatic compounds are available. The Gattermann-Koch reaction employing carbon monoxide, hydrogen chloride, and aluminum chloride, often with a cuprous chloride carrier, is used chiefly for the preparation of benzaldehyde and the mono- and poly-alkylbenzaldehydes.[1] It is unsuccessful with phenols, phenol ethers, and heterocyclic compounds.[1,2]

A second method employs N-methylformanilide and phosphorus oxychloride. It is limited to certain activated compounds such as ethers of the aromatic series,[79] secondary and tertiary aromatic amines,[80] and

[76] Ochiai and Nagasawa, Ber., 72, 1470 (1939).

[77] Wieland and Dorrer, Ber., 58, 818 (1925).

[78] Wieland and Dorrer, Ber., 63, 404 (1930).

[79] Kalischer, Scheyer, and Keller, German pats. 514,415 (1931), and 519,444 (1931) [Chem. Zentr., 102, II, 3394 (1931).]

[80] Vilsmeier and Haack, Ber., 60, 119 (1927).

chloride it reacts as desired.[97] Zinc cyanide that has been washed thoroughly with water and dried does not react, but after addition of sodium chloride or potassium chloride it does react. The amount of catalyst usually used is slightly more than that needed for formation of the hydrogen cyanide adduct.

Solvents. Benzene is frequently used as a solvent particularly where aluminum chloride and a comparatively low reaction temperature are employed. With zinc chloride or in the absence of any catalyst, ether is a desirable solvent in view of its greater solvent action on polyhydric phenols. Furthermore, with ether as a solvent, the primary reaction product, the pure crystalline imine salt, may separate from solution and thus permit isolation before hydrolysis.[11] Chloroform is preferable to ether for the reaction with certain substituted pyrroles.[63] The success of and the orientation obtained in the Gattermann reaction are frequently affected by the nature of the solvent.[56] Tetrachloroethane has been used frequently, as have o-dichlorobenzene and chlorobenzene since they dissolve hydrocarbons, hydrogen cyanide, and final products alike and have high boiling points.

Hydrogen Cyanide. Cylinders of anhydrous hydrogen cyanide can be purchased. The acid can also be prepared readily by treating sodium cyanide with sulfuric acid,[98] or by treating potassium ferrocyanide with sulfuric acid followed by drying by passage over calcium chloride.[99] Detailed directions for the preparation of hydrogen cyanide from sodium cyanide and sulfuric acid are given in *Organic Syntheses*.[100] Cyanogen bromide as a substitute for hydrogen cyanide appears to have little if any advantage.[48]

EXPERIMENTAL PROCEDURES

Mesitaldehyde (hydrogen chloride, zinc cyanide, aluminum chloride, tetrachloroethane as solvent). Detailed directions for the preparation of mesitaldehyde in 75–81% yield from mesitylene are given in *Organic Syntheses*.[58]

4-Methoxy-3-methylbenzaldehyde (hydrogen cyanide, hydrogen chloride, aluminum chloride).[2] *Hydrogen cyanide is extremely poisonous and should be handled with great care. All connections should be thoroughly tested for leaks, and the entire apparatus should be placed in a hood which is in good working order. Rubber gloves should be worn. Adequate ventilation should be maintained at all times. Any vapors escaping from the system*

[97] Arnold and Sprung, *J. Am. Chem. Soc.*, 60, 1699 (1938).

[98] Ziegler, *Ber.*, 54, 110 (1921).

[99] Houben, *Ber.*, 59, 2878 (1926).

[100] Ziegler, *Org. Syntheses*, Coll. Vol. 1, 2nd ed., p. 314, John Wiley & Sons, 1941.

should not be allowed to escape freely, but should be destroyed by passage through solutions of potassium permanganate or hydrogen peroxide. Before handling hydrogen cyanide, one should consult textbooks on the handling of dangerous materials and the treatment and first aid of hydrogen cyanide poisoning.

Gaseous hydrogen chloride is passed for one-half hour through a mixture of 25 g. (0.93 mole) of anhydrous hydrogen cyanide and 30 g. (0.25 mole) of o-cresyl methyl ether cooled in an ice bath. Aluminum chloride, 30 g. (0.22 mole), is added gradually. While slowly adding more hydrogen chloride, the temperature is raised to 45° and kept there for four to five hours. The reaction mixture is poured over ice and hydrochloric acid. The resulting copious precipitate is heated under reflux with hydrochloric acid. The aldehyde is steam-distilled and then treated with sodium bisulfite solution. The bisulfite addition product is filtered and decomposed with aqueous sodium carbonate. The yield of colorless oil, b.p. 251°, is 30–37 g. (80–100%).

4-Hydroxy-2,6-dimethylbenzaldehyde (hydrogen chloride, hydrogen cyanide, aluminum chloride, benzene as solvent).[3] To an ice-cooled solution of 20 g. (0.16 mole) of 3,5-dimethylphenol in 80 ml. of benzene is added 13.8 g. (0.51 mole) of dry hydrogen cyanide. This is followed by 30 g. (0.22 mole) of aluminum chloride. After hydrogen chloride has been passed through the mixture for four hours at a temperature of 35°, it is poured into a mixture of hydrochloric acid and ice. Benzene is removed by steam distillation, and the residue is extracted with ether. The resulting ethereal solution is extracted with sodium bisulfite solution. After the aqueous layer has been washed with ether, it is acidified with dilute sulfuric acid. The precipitated aldehyde is crystallized from ethanol in the form of long yellow needles, m.p. 189–190°, in an almost quantitative yield.

2-Hydroxy-1-naphthaldehyde (hydrogen chloride, hydrogen cyanide, zinc chloride, anhydrous ethyl ether as solvent).[4] To a well-cooled mixture of 15 g. (0.10 mole) of 2-naphthol, 45 ml. of ether, and 6.9 g. (10 ml., 0.26 mole) of dry hydrogen cyanide is added 15 g. (0.11 mole) of anhydrous zinc chloride. Anhydrous hydrogen chloride is passed through this mixture at room temperature for two and one half hours. During this time a dark oil settles to the bottom and eventually solidifies. The solid is washed thoroughly with ether and then heated for a short time with water. The oily material, which crystallizes in almost quantitative yield on cooling, melts at 81° after crystallization from dilute ethanol.

2,4-Dihydroxybenzaldehyde (hydrogen chloride, hydrogen cyanide from potassium ferrocyanide and sulfuric acid, anhydrous ethyl ether as solvent).[44] Potassium ferrocyanide (200 g.) is heated in a flask with a

mixture of 160 g. of concentrated sulfuric acid and 280 ml. of water. The evolved hydrogen cyanide is led from the flask by means of an air condenser and passed through a calcium chloride drying train kept at 35–40° (hydrogen cyanide liquefies at 26°), and into a flask kept at −5° that contains 1 part of resorcinol dissolved in 3 parts of anhydrous ether. When the increase in weight indicates a 50% excess of hydrogen cyanide, hydrogen chloride is led slowly through the same drying train until it ceases to be absorbed by the ether solution. The semisolid reaction mixture is allowed to stand for several hours, after which it is decomposed with boiling water. The resulting mixture is filtered, and, on cooling, crystals of the aldehyde separate in good yield.

2,4-Dihydroxy-6-methylbenzaldehyde (hydrogen chloride, zinc cyanide, anhydrous ethyl ether as solvent).[5] A 500-ml. three-necked round-bottomed flask is fitted with a stirrer, a reflux condenser, and an inlet tube having a wide mouth to prevent clogging and extending nearly to the bottom of the flask. A safety bottle is placed in series with this tube and a dry hydrogen chloride generator. The top of the condenser connects to a tube leading into a wash bottle containing sulfuric acid, then to a safety bottle, and finally to the surface of aqueous sodium hydroxide. To the reaction flask, containing 20 g. (0.16 mole) of thoroughly dried orcinol (freed of water of crystallization) and 200 ml. of dry ether, is added 28.1 g. (0.24 mole) of dry zinc cyanide. The mechanical stirrer is started, and dry hydrogen chloride is passed in rapidly. A pink color develops, and the condensation product begins to separate as a thick oil. After about one and one half hours, the ether becomes saturated with hydrogen chloride; the hydrogen chloride is then passed in more slowly for an additional half hour. After the ether is decanted, the solid residue is boiled for two to three minutes with about 100 ml. of water. The hot solution is filtered and cooled to yield a crystalline product (85%) which, after crystallization from water, melts at 178–180°.

p-Anisaldehyde (hydrogen chloride, zinc cyanide, aluminum chloride, benzene as solvent).[6] The same type of apparatus may be employed for this preparation as was used above for the preparation of 2,4-dihydroxy-6-methylbenzaldehyde. To a mixture of 30 g. (30.1 ml., 0.28 mole) of anisole and 75 ml. of dry benzene is added 52 g. (0.44 mole) of dry zinc cyanide. Dry hydrogen chloride is added rapidly to the cooled and continuously stirred mixture for thirty to sixty minutes. Anhydrous aluminum chloride (49 g., 0.34 mole) is added slowly and with further cooling and stirring. This is followed by a slow stream of hydrogen chloride which is added while the mixture is heated at 40–45° for three to four hours. The contents of the flask are added to an excess of 10% hydrochloric acid, which generally causes a heavy precipitate to separate.

The resulting mixture is heated under reflux for one-half hour, and the aldehyde is steam-distilled. The steam distillate is extracted with benzene, and the benzene is subsequently removed by distillation. The residue is shaken with sodium bisulfite solution, and the anisole is extracted with ether. The aldehyde is released from the bisulfite addition product by warming with aqueous sodium carbonate. The yield of aldehyde, boiling at 246–248°, is 94%.

p-Toluicaldehyde (hydrogen chloride, hydrogen cyanide, aluminum chloride, toluene as solvent).[8] To a mixture of 52 g. (0.39 mole) of aluminum chloride and 50 ml. of toluene cooled in ice is added with shaking 10.3 g. (15 ml., 0.38 mole) of dry hydrogen cyanide during a period of fifteen minutes. After being kept at room temperature for five minutes, the mixture is heated to about 60° and a slow current of hydrogen chloride is passed through. A vigorous reaction occurs, and the mixture is maintained at 100° for two hours while hydrogen chloride is introduced and an additional three hours at 100° after the flow of hydrogen chloride is stopped. The reaction mixture is kept at room temperature overnight. After the viscous mixture is poured over a mixture of ice and concentrated hydrochloric acid, the resulting organic layer is steam-distilled. From the dried ethereal extract of the distillate, the aldehyde is obtained in quantitative yield by fractional distillation; b.p. 200–204°.

3,5-Dimethylpyrrole-2-carboxaldehyde (hydrogen chloride, hydrogen cyanide, chloroform as solvent).[63] To a solution of 4 g. (0.03 mole) of 2,4-dimethylpyrrole in 40 ml. of chloroform that has been previously dried with phosphorus pentoxide is added 5.5 g. (0.2 mole) of dry hydrogen cyanide. The mixture is cooled with an ice bath, and dry hydrogen chloride is introduced for one hour. Without attempting to filter the crystals, the solvent is removed under reduced pressure at room temperature, and the residue is dissolved in cold water. Sodium hydroxide is added, ammonia is evolved, and the aldehyde separates as dark yellow crystals of melting point 89°; yield, 92%.

TABULAR SURVEY OF ALDEHYDES PREPARED BY THE GATTERMANN REACTION

In the following tables an attempt has been made to cover the syntheses of aromatic aldehydes by the Gattermann reaction reported in the literature to January 1, 1954. The first column in the tables lists the aldehydes formed, the second column the reagents and solvents, without parentheses. Also in the second column is listed in parentheses the starting material wherever it is not obvious.

Table I lists compounds obtained from aromatic hydrocarbons, chlorobenzene, and aniline. Usually the substituted benzaldehyde formed is

indicated merely by the substituent groups. Table II gives the aldehydes derived from phenols and phenol ethers; Table III lists the aldehydes obtained from naphthols, naphthol ethers, and phenanthrol. Heterocyclic aldehydes are listed in Table IV; and compounds that did not yield aldehydes are shown in Table V.

The reagents are listed as A, B, C, D, E, and F as defined below:

A: HCl, HCN.

B: HCl, HCN, $ZnCl_2$.

C: HCl, HCN, $AlCl_3$.

D: HCl, NaCN, $AlCl_3$.

E: HCl, $Zn(CN)_2$, $AlCl_3$.

F: HCl, $Zn(CN)_2$.

TABLE I

Aldehydes Prepared from Aromatic Hydrocarbons

Substituent(s) in Benzaldehyde or Complete Name of Aldehyde	Reagents	Yield, %	Reference
Benzaldehyde	D	11	60
	C	—	57
		16–39	8
	C, CHCl$_2$CHCl$_2$	75	7
4-Amino-	A, ether (aniline)	—	61
4-Chloro-	C	8	7
4-Methyl-	D	39	9
		20	60
	C	—	57
		14–91	10
		14–quant.	8
4-Ethyl-	D	27	9
		38	60
	C	30	56
	C, C$_6$H$_5$Cl	22	7
	C, CHCl$_2$CHCl$_2$	5	7
4-Isopropyl-	D	24	60
4-s-Butyl-	D	4	60
4-t-Amyl-	D	8	60
4-Phenyl-	C, CHCl$_2$CHCl$_2$	75	7
2,4-Dimethyl-	C	—	57
		97	8
	D	26	56
	D, (o-xylene)	75	56
	D, (p-xylene)	17	56
2,5-Dimethyl-	C	85	8
3,4-Dimethyl-	C	85	8
	D	42	9
Diethyl-	D, (ethylbenzene)	13	56
	C, (ethylbenzene)	25	56
2-Isopropyl-5-methyl-	D	25	56
Isopropyl-methyl-	D, (p-cymene)	5–17	56
Diisopropyl-	D, (isopropylbenzene)	12–18	9, 56
	D, (m-diisopropylbenzene)	17–39	56
	D, (p-cymene)	13	56
3,4-Trimethylene-	C, CHCl$_2$CHCl$_2$ (hydrindene)	45–60	7

TABLE I—*Continued*
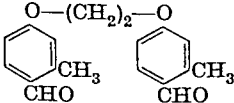
ALDEHYDES PREPARED FROM AROMATIC HYDROCARBONS

Substituent(s) in Benzaldehyde or Complete Name of Aldehyde	Reagents	Yield, %	Reference
3,4-Tetramethylene-	C, $CHCl_2CHCl_2$ (tetralin)	4	7
	C, C_6H_6 (tetralin)	33	3
2,3,5-Trimethyl-	D, (mesitylene)	13	56
2,4,5-Trimethyl-	D	7	56
	D, (m-xylene)	13	56
	D, (p-xylene)	21	56
2,4,6-Trimethyl-	C, $CHCl_2CHCl_2$	67–83	7
	E, $CHCl_2CHCl_2$	75–81	58, 59
	D, (1,2,4-trimethylbenzene)	7	56
2,4,6-Triethyl-	E, $CHCl_2CHCl_2$	69	58, 59
Triethyl-	D, (ethylbenzene)	5	56
Diisopropyl-methyl-	D, (p-cymene)	10–16	56
2,4,6-Triisopropyl-	E, $CHCl_2CHCl_2$	65	58, 59
Triisopropyl-	D, (m-diisopropylbenzene)	5–16	56
2-Fluorenecarbox-aldehyde	C, $CHCl_2CHCl_2$	52–70	7
	C, C_6H_5Cl	76	7
	C, o-$C_6H_4Cl_2$	62	7
1-Naphthaldehyde	C, C_6H_5Cl	31–60	7
	C, $CHCl_2CHCl_2$	66	7
4-Methyl-1-naphth-aldehyde	C, o-$C_6H_4Cl_2$	51	7
2,3-Dimethyl-1-naphthaldehyde	E, $CHCl_2CHCl_2$	38	59
2,6-Dimethyl-1-naphthaldehyde	C, C_6H_5Cl	60·	7
4,7-Dimethyl-1-naphthaldehyde	C, C_6H_5Cl	58	7
5-Acenaphthenecarbox-aldehyde	C, $CHCl_2CHCl_2$	70–90	7
9-Anthracenecarbox-aldehyde	C, $CHCl_2CHCl_2$	50	7
	C, C_6H_5Cl	60	7
9-Phenanthrenecarbox-aldehyde	C, C_6H_5Cl	44	7

TABLE II

ALDEHYDES PREPARED FROM PHENOLS AND THEIR ETHERS

A. Aldehydes Prepared from Monohydric Phenols or Their Ethers

Substituent(s) in Benzaldehyde or Complete Structural Formula	Reagents	Yield, %	Reference
4-Hydroxy-	C, C_6H_6	30	3, 19
4-Methoxy-	D	43	9
	C	45–89	2, 3, 8
	$Zr(CN)_2$, $ZrCl_4$, C_6H_6	Poor	18
	E, C_6H_6	94	6
4-Ethoxy-	C	80	2, 3
4-(β-Bromoethoxy)-	C, C_6H_6	50	3
4-Phenoxy-	C or E, C_6H_6	50–80	3, 6, 101
$(-CH_2OC_6H_4CHO\text{-}p)_2$	C, C_6H_6	—	3
$CH_2(-CH_2OC_6H_4CHO\text{-}p)_2$	C, C_6H_6	30	3
4-(4'-Methoxyphenoxy)-	C, C_6H_6	6	54
2-Bromo-4-hydroxy-	C, C_6H_6	10	3
2-Bromo-4-ethoxy-	C, C_6H_6	—	3
2-Chloro-4-hydroxy-	C, C_6H_6	50	3
2-Chloro-4-methoxy-	C, C_6H_6	—	3
2-Chloro-4-ethoxy-	C, C_6H_6	80	3
3-Chloro-4-methoxy-	C	ca. 80	2
	C, C_6H_6	—	3
2-Hydroxy-4-methyl-	E, C_6H_6	Small	22
2-Hydroxy-5-methyl-	C, C_6H_6	5	3
2-Methoxy-5-methyl-	E, C_6H_6	80	6
	C, with or without benzene	ca. 80	2, 3
2-Ethoxy-5-methyl-	C, C_6H_6	80	3
4-Hydroxy-2-methyl-	E, C_6H_6	30	22
	C, C_6H_6	45–50	3, 19
	E, C_6H_6 (2-isopropyl-5-methylphenol)	Small	20
4-Methoxy-2-methyl-	C	ca. 80	2, 3
4-Ethoxy-2-methyl-	C	90	3
$O-(CH_2)_2-O$	C, C_6H_6	33	3

[101] Slotta and Soremba, *Ber.*, 68, 2059 (1935).

TABLE II—*Continued*

A. *Aldehydes Prepared from Monohydric Phenols or Their Ethers—Continued*
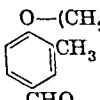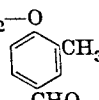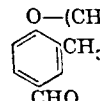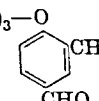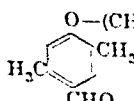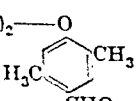
Substituent(s) in Benzaldehyde or Complete Structural Formula	Reagents	Yield, %	Reference
4-Hydroxy-3-methyl-	C or E, C_6H_6	35–40	3, 6, 19
	E, C_6H_6 (2-methyl-5-isopropylphenol)	Small	20
4-Hydroxy-3-ethyl-	C, C_6H_6	65	3
4-Methoxy-3-ethyl-	C	90	2, 3
4-Ethoxy-3-ethyl-	C	80	2, 3
4-(β-Bromoethoxy)-3-ethyl-	C, C_6H_6	50	3
O—$(CH_2)_2$—O (bis-ring structure with CH_3 and CHO groups)	C, C_6H_6	Almost quant.	3
O—$(CH_2)_3$—O (bis-ring structure with CH_3 and CHO groups)	C, C_6H_6	ca. 33	3
2-Hydroxy-3,4-dimethyl-	C	Small	18
2-Hydroxy-4,5-dimethyl-	C, C_6H_6	—	3
2-Hydroxy-6-isopropyl-3-methyl-	E, C_6H_6	Small	20
2-Hydroxy-3-isopropyl-6-methyl-	E, C_6H_6	Small	20
4-Hydroxy-2,3-dimethyl-	C, C_6H_6	60	3
	C	—	18
	C, (2,3,4-trimethylphenol)	52	18
4-Hydroxy-2,5-dimethyl-	C, C_6H_6	80	3
4-Hydroxy-5-isopropyl-2-methyl-	C or E, C_6H_6	Almost quant.	3, 6, 19, 20, 21
4-Hydroxy-2-isopropyl-5-methyl-	C, C_6H_6	30	3
	E, C_6H_6	Good	20, 21
O—$(CH_2)_2$—O (bis-ring structure with H_3C, CH_3 and CHO groups)	C, C_6H_6	66	3
4-Hydroxy-2,6-dimethyl-	C, C_6H_6	Almost quant.	3

TABLE II—*Continued*

A.   Aldehydes Prepared from Monohydric Phenols or Their Ethers—Continued

Substituent(s) in Benzaldehyde or Complete Structural Formula	Reagents	Yield, %	Reference
4-Methoxy-2,6-dimethyl-	B, ether	—	3
4-Ethoxy-2,6-dimethyl-	B, ether	Almost quant.	3
4-Hydroxy-3,5-dimethyl-	C, C_6H_6	—	3
	C, (2,6-dimethylanisole)	Main product	3
	C, C_6H_6 (2,4,6-trimethylanisole)	—	18
4-Methoxy-3,5-dimethyl-	C	Poor*	3
4-Ethoxy-3,5-dimethyl-	C	Moderate*	3
2-Hydroxy-3,4,5-trimethyl-	C	Small	18
3-Hydroxy-2,4,6-trimethyl-	C, (mesityl methyl ether)	—	18

* This reaction involved some cleavage of the ether group.

TABLE II—*Continued*
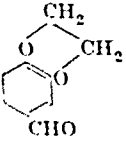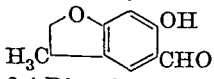
B. *Aldehydes Prepared from Dihydric Phenols or Their Ethers*

Substituent(s) in Benzaldehyde or Complete Structural Formula	Reagents	Yield, %	Reference
2,4-Dihydroxy-	A or F, ether	56–97	3, 5, 11, 41, 43, 44
	HCONH$_2$, POCl$_3$, ether	—	50
	C	Almost quant.	19
		69–82	8
	BrCN, HCl, ZnCl$_2$, ether	—	48
4-Hydroxy-2-methoxy-	C, C$_6$H$_6$	75	3
	C	80	19
2,4-Dimethoxy-	C or E, C$_6$H$_6$	80–almost quant.	3, 6
	C	ca. 80	2
2-Ethoxy-4-methoxy- and 4-ethoxy-2-methoxy-	B, ether	26 and 32, resp.	53
2-Methoxy-4-n-propoxy- and 4-methoxy-2-n-propoxy-	B, ether	26 and 26, resp.	53
4-Allyloxy-2-methoxy- and 2-allyloxy-4-methoxy-	B, ether	32 and 16, resp.	53
4-Benzyloxy-2-methoxy- and 2-benzyloxy-4-methoxy-	B, ether	Total yield, 40	53
4-Methoxy-2-phenoxy- and 2-methoxy-4-phenoxy-	C, C$_6$H$_6$	Total yield, 40–45	54
2,5-Dimethoxy-	C, C$_6$H$_6$	—	3
2,5-Diethoxy-	C, C$_6$H$_6$	—	3
3,4-Dimethoxy-	C	ca. 80	2
	C, C$_6$H$_6$	60	3
3,4-Diethoxy-	C, C$_6$H$_6$	75	3
	C, C$_6$H$_6$	—	3
4-Methoxy-3-phenoxy- and 4-(2'-methoxyphenoxy)-	C, C$_6$H$_6$	40–45	54

<div align="center">

TABLE II—*Continued*
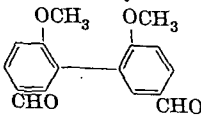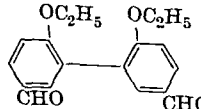
B. Aldehydes Prepared from Dihydric Phenols or Their Ethers—Continued

</div>

Substituent(s) in Benzaldehyde or Complete Structural Formula	Reagents	Yield, %	Reference
2,4-Dihydroxy-3-ethyl-	F	—	37
	A, ether	—	46
2,4-Dihydroxy-3-formyl-	E, ether (2,4-dihydroxybenzaldehyde)	10	28
2,4-Dihydroxy-3-nitro-	E, ether	—	26
3-Acetyl-2,4-dimethoxy-	C, ether	—	25
	E, ether	80	32
2,4-Dihydroxy-5-methyl-	C, C_6H_6	90	3
2,4-Dihydroxy-5-ethyl-	C, C_6H_6	Almost quant.	3
5-Carbomethoxy-2,4-dihydroxy-	F, ether	53	102
	B, ether	—	51
2,4-Dimethoxy-5-methyl-	C, C_6H_6	Almost quant.	3
2,4-Dihydroxy-6-methyl-	A, ether	93	3, 41
	C	Quant.	2
	F, ether	85	5
4-Hydroxy-2-methoxy-6-methyl-	C, C_6H_6	—	3
2,4-Dimethoxy-6-methyl-	C, C_6H_6	63	3
3-Acetyl-2,6-dihydroxy-	C, ether	—	25
	E, ether	45	30
2,6-Dihydroxy-3-propionyl-	E, KCl, $CH_3CO_2C_2H_5$, ether	64	33
3-n-Butyryl-2,6-dihydroxy-	E, KCl, $CH_3CO_2C_2H_5$, ether	26	33
3-Benzoyl-2,6-dihydroxy-	E, KCl, $CH_3CO_2C_2H_5$, ether	36	33
	C, ether	—	25
3-Carbomethoxy-2,6-dihydroxy-	C, ether	ca. 30	24
	E, ether	65	29
2,6-Dihydroxy-3-nitro-	E, ether	—	26

[102] Mody and Shah, *Proc. Indian Acad. Sci.*, **34A**, 77 (1951) [*C. A.*, **46**, 11189 (1952)].

TABLE II—*Continued*

B. *Aldehydes Prepared from Dihydric Phenols or Their Ethers—Continued*

Substituent(s) in Benzaldehyde or Complete Structural Formula	Reagents	Yield, %	Reference
4,5-Dimethoxy-2-methyl-	C, C_6H_6	Almost quant.	3
5-Ethoxy-4-methoxy-2-methyl-	C, C_6H_6	—	3
Chloro-dihydroxy-	C, C_6H_6	Almost quant.	3
2,6-Dihydroxy-3,5-dimethyl-	F, ether	—	39
Acetyl-2,6-dihydroxy-3-phenyl-	E, KCl, $CH_3CO_2H_5$, ether	51	33
3-Acetyl-5-ethyl-2,6-dihydroxy-	E, ether	38	32
3-Carbomethoxy-5-ethyl-2,6-dihydroxy-	E, ether	57	31
3-Formyl-2,6-dihydroxy-4-methyl- or 3-formyl-2,4-dihydroxy-6-methyl-	E, ether (2,4-dihydroxy-6-methylbenzaldehyde)	—	27
	E, KCl, ether (2,4-dihydroxy-6-methyl-benzaldehyde)	11	28
3-Acetyl-2,6-dihydroxy-4-methyl-	C, ether	—	25
	E, ether	26	32
3-Carbomethoxy-2,6-dihydroxy-4-methyl- or carbethoxy- analog	E, ether	Almost quant.	34
3-Ethyl-4,6-dihydroxy-2-methyl-	F, ether	51	39
2,5-Dihydroxy-3,4,6-trimethyl-	E, C_6H_6	47	103
3,5-Diethyl-2,6-dihydroxy-4-methyl-	F, ether	52	39
5-Carbethoxy-2,4-dihydroxy-3,6-dimethyl-	E, ether	62	34
	C, C_6H_6	—	3
	C, C_6H_6	50	3

[103] Smith and King, *J. Am. Chem. Soc.*, **63**, 1889 (1941).

TABLE II—*Continued*

C. *Aldehydes Prepared from Trihydric and Tetrahydric Phenols or Their Ethers*

Substituent(s) in Benzaldehyde	Reagents	Yield, %	Reference
2,3,4-Trihydroxy-	C, C_6H_6		
	B, ether	—	19
2,4-Dihydroxy-3-methoxy-	F, ether	50	3, 41
2,4,5-Trihydroxy-	F, ether	45	5
	B, ether	93	40
2,5-Dihydroxy-4-methoxy-	A, $Zn(CN)_2$, ether	Almost quant.	3, 41
2-Hydroxy-4,5-dimethoxy-	A, $Zn(CN)_2$, ether	39	35
4-Ethoxy-2-hydroxy-5-methoxy-	A, $Zn(CN)_2$, ether	85	35
5-Ethoxy-2-hydroxy-4-methoxy-	A, $Zn(CN)_2$, ether	86	35
2,4,5-Trimethoxy-	A, $Zn(CN)_2$, ether	71	35
2,4,6-Trihydroxy-	C, C_6H_6	Very good	52
	A, ether	Good	3, 41
	BrCN, HCl, $ZnCl_2$, ether	—	48
2,4-Dihydroxy-6-methoxy- or 2,6-dihydroxy-4-methoxy-	B, ether		
6-Ethoxy-2,4-dihydroxy-	A, ether	—	42
3-Ethyl-2,4,6-trihydroxy-	A, ether	97	45
3-Formyl-2,4,6-trihydroxy-	F, ether (phloroglucinol)	78	47
3-Acetyl-2,4,6-trihydroxy-	E, ether	2	38
		32	28
2,6-Dihydroxy-4-methoxy-3-methyl-	C, ether	51	32
4-Ethoxy-2,6-dihydroxy-3-methyl-	E, ether	—	25
3-Formyl-2,4-dihydroxy-6-methoxy-	A, ether	72	28
6-Hydroxy-2,4-dimethoxy-3-methyl-	E, ether (2,4-dihydroxy-6-methoxybenzaldehyde)	71	45
		13	28
3-Formyl-2-hydroxy-4,6-dimethoxy-	A		
3-Acetyl-2-hydroxy-4,6-dimethoxy-	E, ether (2-hydroxy-4,6-dimethoxybenzaldehyde)	56	45
		21 crude	28
	E, ether		

TABLE II—*Continued*

*C. Aldehydes Prepared from Trihydric and Tetrahydric Phenols
or Their Ethers—Continued*

Substituent(s) in Benzaldehyde	Reagents	Yield, %	Reference
3-Formyl-2,4,6-trihydroxy-5-methyl-	A, ether (methylphloroglucinol)	7	38
5-Ethyl-3-formyl-2,4,6-trihydroxy-	A, ether (ethylphloroglucinol)	24	38
5-*i*-Amyl-3-formyl-2,4,6-trihydroxy-	A, ether (*i*-amylphloroglucinol)	15	38
3,5-Dicarbethoxy-2,4,6-trihydroxy-	E, KCl, ether	85 crude	28
2,4-Dihydroxy-3,6-dimethoxy-	F, ether (1,4-dimethoxy-2,6-dibenzoxybenzene)	— 79	36 36

TABLE IV

ALDEHYDES PREPARED FROM HETEROCYCLIC COMPOUNDS

Product	Reagents	Yield, %	Reference
2-Furfural	A, ether	35	74
3-Methyl-2-furfural	A, ether	56	105
5-Methyl-2-furfural	A, ether	60	74
5-Ethyl-2-furfural	A, ether	53	74
3,5-Dimethyl-2-furfural	A, ether	12	105
$\left[-H_2C\diagdown_O\diagup CHO\right]_2$	A, ether	Poor	74
6-Hydroxybenzofuran-5-carboxaldehyde	B, ether	—	51
6-Hydroxy-3-methylbenzofuran-5-carboxaldehyde	B, ether	—	51
6-Hydroxy-3,4-dimethyl-benzofuran-5-carboxaldehyde	B, ether	—	42
4,6-Dimethoxybenzofuran-7-carboxaldehyde	A, ether	9	75
2-Carbethoxy-4,6-dimethoxy-benzofuran-7-carboxaldehyde	C, ether	90	75
	B, ether	72	75
Dibenzofuran-3-carboxaldehyde	C, $CHCl_2CHCl_2$ (o,o′-dihydroxy-biphenyl)	81	55
2-Thiophenecarboxaldehyde	C	8	64
1-Methylpyrrole-2-carbox-aldehyde	A, ether, $CHCl_3$	31	64
1-n-Butylpyrrole-2-carbox-aldehyde	A, ether	61	64
1-i-Amylpyrrole-2-carbox-aldehyde	A, ether	62	64
1-(2′-Furfuryl)-pyrrole-2-carboxaldehyde	A, ether	16	64
5-Phenylpyrrole-2-carbox-aldehyde	F, ether	—	72
5-Carbethoxypyrrole-2-carboxaldehyde	A, $CHCl_3$, ether	28	64
3,4-Dimethylpyrrole-2-carboxaldehyde	A, ether	—	106

[105] Reichstein, Zschokke, and Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).
[106] Fischer and Hofelmann, *Ann.*, **533**, 225 (1930).

TABLE IV

Aldehydes Prepared from Heterocyclic Compounds

Product	Reagents	Yield, %	Reference
2-Furfural	A, ether	35	74
3-Methyl-2-furfural	A, ether	56	105
5-Methyl-2-furfural	A, ether	60	74
5-Ethyl-2-furfural	A, ether	53	74
3,5-Dimethyl-2-furfural	A, ether	12	105
$\left[-\text{H}_2\text{C}\underset{\text{O}}{\bigcirc}\text{CHO}\right]_2$	A, ether	Poor	74
6-Hydroxybenzofuran-5-carboxaldehyde	B, ether	—	51
6-Hydroxy-3-methylbenzofuran-5-carboxaldehyde	B, ether	—	51
6-Hydroxy-3,4-dimethylbenzofuran-5-carboxaldehyde	B, ether	—	42
4,6-Dimethoxybenzofuran-7-carboxaldehyde	A, ether	9	75
2-Carbethoxy-4,6-dimethoxybenzofuran-7-carboxaldehyde	C, ether	90	75
	B, ether	72	75
Dibenzofuran-3-carboxaldehyde	C, CHCl$_2$CHCl$_2$	81	55
2-Thiophenecarboxaldehyde	C (o,o'-dihydroxybiphenyl)	8	64
1-Methylpyrrole-2-carboxaldehyde	A, ether, CHCl$_3$	31	64
1-n-Butylpyrrole-2-carboxaldehyde	A, ether	61	64
1-i-Amylpyrrole-2-carboxaldehyde	A, ether	62	64
1-(2'-Furfuryl)-pyrrole-2-carboxaldehyde	A, ether	16	64
5-Phenylpyrrole-2-carboxaldehyde	F, ether	—	72
5-Carbethoxypyrrole-2-carboxaldehyde	A, CHCl$_3$, ether	28	64
3,4-Dimethylpyrrole-2-carboxaldehyde	A, ether	—	106

[105] Reichstein, Zschokke, and Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).
[106] Fischer and Höfelmann, *Ann.*, **533**, 225 (1930).

TABLE IV—*Continued*

ALDEHYDES PREPARED FROM HETEROCYCLIC COMPOUNDS

Product	Reagents	Yield, %	Reference
3,5-Dimethylpyrrole-2-carboxaldehyde	A, $CHCl_3$	92	63
	A, ether	Moderate	63
	$HCONH_2$, $POCl_3$	—	50
4-Bromo-3,5-dimethylpyrrole-2-carboxaldehyde	A, ether	22	67
4-Ethyl-3,5-dimethylpyrrole-2-carboxaldehyde	A, $CHCl_3$	8	107
3-Carbethoxy-4,5-dimethyl-pyrrole-2-carboxaldehyde	A, ether	—	109
4-Carbethoxy-3,5-dimethyl-pyrrole-2-carboxaldehyde	A, ether	95	68
4-Acetyl-3,5-dimethylpyrrole-2-carboxaldehyde	A, ether or $CHCl_3$	65	62
5-Ethyl-3-methyl-4-propionyl-pyrrole-2-carboxaldehyde	A, ether	—	109
H_3C⌐⌐CH_3 OHC⌐N⌐$CH{=}C(CN)CO_2CH_3$ H	A, $CHCl_3$, ether	35	106
2,4,5-Trimethylpyrrole-3-carboxaldehyde	A, $CHCl_3$	67	63
5-Ethyl-2,4-dimethylpyrrole-3-carboxaldehyde	A, H_2O	77	108
5-Carbethoxy-2,4-dimethyl-pyrrole-3-carboxaldehyde	A, ether	85	69
	$HCONH_2$, $POCl_3$, ether	—	50
4-Carbethoxy-2,5-dimethyl-pyrrole-3-carboxaldehyde	A, ether	77	68
	$HCONH_2$, $POCl_3$, ether	—	50
4-Carbethoxy-1,2,5-trimethyl-pyrrole-3-carboxaldehyde	A, ether	ca. 90	70
4-Carbethoxy-2,5-dimethyl-1-*p*-tolylpyrrole-3-carbox-aldehyde	A, ether	80–90	70

[107] Fischer and Schubert, *Ber.*, **56**, 1202 (1923).
[108] Fischer and Walach, *Ann.*, **447**, 38 (1926).
[109] Fischer and Klarer, *Ann.*, **447**, 48 (1926).

TABLE IV—*Continued*

ALDEHYDES PREPARED FROM HETEROCYCLIC COMPOUNDS

Product	Reagents	Yield, %	Reference
4-Carbethoxy-1-phenyl-2,5-dimethylpyrrole-3-carboxaldehyde	A, ether	80–90	70
2-Methylindole-3-carboxaldehyde	B, ether	75	71
	F, ether	19	73
	A, $CHCl_3$	90	66
	A, ether	87	65
2-Carbethoxyindole-3-carboxaldehyde	A, $CHCl_3$	—	66
	F, ether	83	73
2-Carbethoxy-7-methylindole-3-carboxaldehyde	F, ether	Good	73
2-Hydroxy-4-methylthiazole-4-carboxaldehyde	A, ether, $CHCl_2CHCl_2$	25	76

TABLE V

COMPOUNDS THAT DID NOT YIELD ALDEHYDES

Starting Material	Reference	Starting Material	Reference
Indene*	7	o-Methoxybiphenyl†	55
Nitrobenzene†	55	Pyrrole*	64
2-Nitrophenol†	55	2-Carboxypyrrole*	64
Benzoic Acid†	55	2-Acetylpyrrole‡	64
Cinnamic Acid†	55	Indole	66
Aniline†	55	Furfuryl methyl ether*	74
Diphenylamine†	55	Difurfuryl ether*	74
N,N-Dimethylaniline†	55	2-Carbomethoxy-4,7-dimethoxy-6-hydroxy-benzofuran	36
Azobenzene†	55		
Benzophenone†	55	4-Methylthiazole‡	76
Anthraquinone†	55	Benzofuran‡	74
1,5-Dihydroxyanthraquinone†	55	Ethyl 2-furoate‡	74
o-Hydroxybiphenyl†	55	2-Acetylfuran‡	74

* A polymeric solid was formed.
† The starting material was recovered or a polymeric solid was formed.
‡ The starting material was recovered.

CHAPTER 3

THE BAEYER-VILLIGER OXIDATION OF ALDEHYDES AND KETONES

C. H. Hassall

University College of the West Indies, Jamaica

CONTENTS

INTRODUCTION

In 1899, Baeyer and Villiger[1] showed that the oxidation of the alicyclic ketones menthone, tetrahydrocarvone (I), and camphor with permonosulfuric acid led to the formation of lactones.

$$\text{I} \qquad \xrightarrow{\text{HO}_2\text{SO}_3\text{H}} \qquad$$
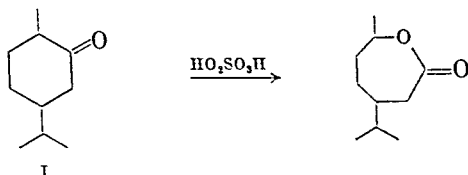
Further studies, using a variety of ketones or aldehydes and hydrogen peroxide or peracids in various media, have established that the oxidation represented by the following equation is of wide applicability.

$$\begin{array}{ccc} \text{R}-\overset{\|}{\underset{\text{O}}{\text{C}}}-\text{R}' & \xrightarrow{\text{H}_2\text{O}_2 \text{ or peracid}} & \text{R}-\overset{\|}{\underset{\text{O}}{\text{C}}}-\text{OR}' \end{array}$$
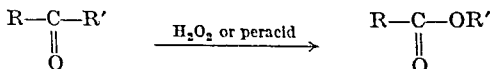
This oxidation, the Baeyer-Villiger reaction, is the subject of this review. As the oxidation normally employs mild conditions, gives reasonable yields, and shows a high degree of selectivity, it has proved useful in a variety of both synthetic and degradative studies. Recent investigations have led to a better definition of favorable experimental conditions and have extended appreciably the scope of the reaction.

MECHANISM OF THE REACTION

It is now generally agreed that the Baeyer-Villiger reaction is ionic in character. The favored reaction pattern was first outlined by Criegee in 1948.[2] It assumes that in the first instance addition of the peroxide to the carbonyl group yields a hydroxyperoxide (A). This dissociates to give an electron-deficient ion (B), which rearranges to C with cleavage of a carbon-carbon bond. The postulated carbonium ion C decomposes to the ester D in a normal way.

This mechanism has recently been the subject of detailed discussion by a number of authors.[3-9] The scheme accounts for the observation that in the oxidation of substituted acetophenones with perbenzoic acid the

[1] Baeyer and Villiger, Ber., 32, 3625 (1899).

[2] Criegee, Ann., 560, 127 (1948).

supported by the observation that fluorenone peroxide, formulated as IV, rearranged to the lactone V on heating.[14] There is now evidence that fluorenone peroxide is a molecular complex of fluorenone and fluorenone hydroperoxide.[15] There is no evidence for the existence of stable "oxoxides."

     IV   V
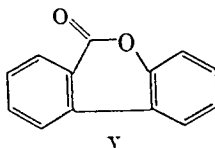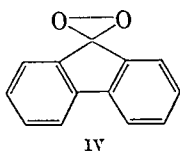
It has been postulated that hydroxyl radicals may participate in the oxidation by interacting with the enolic form of the ketone.[16] It is unlikely that such a step is involved in the Baeyer-Villiger reaction, as many ketones that are not capable of enolization undergo the reaction. Also, in cases where it is established that attack on enols takes place, hydroxylation and not Baeyer-Villiger oxidation occurs.[17] It has been shown that unsaturated ketones may undergo Baeyer-Villiger oxidation without the olefinic bonds being attacked.[18] This would not be expected if free hydroxyl radicals were involved.[19]

SCOPE OF THE REACTION

Saturated Aliphatic Ketones. There is only one example of the Baeyer-Villiger oxidation of a simple ketone of the type RCH_2COCH_2R' to an ester. Methyl n-hexyl ketone gives n-hexyl acetate (VI) and its hydrolysis products on treatment with hydrogen peroxide in hydrofluoric acid.[20]

$$CH_3(CH_2)_5COCH_3 \xrightarrow[HF]{H_2O_2} CH_3(CH_2)_5OCOCH_3 + CH_3CO_2H + CH_3(CH_2)_5OH$$
$$VI$$
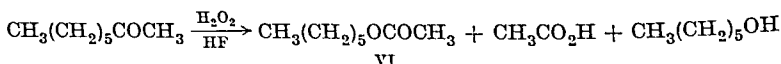
It has been shown that hydrogen peroxide in the presence of sulfuric acid may oxidize such ketones to ketone peroxides and α-ketols.[21] Perbenzoic acid is said to have no significant action.[22] However, as peracids have not yet been used under the most favorable conditions there is no decisive evidence that they will not react with these simple ketones.

[14] Wittig and Pieper, *Ber.*, **73**, 295 (1940).
[15] Criegee, Schnorrenberg, and Becke, *Ann.*, **565**, 7 (1949).
[16] Böeseken, *Proc. Acad. Sci. Amsterdam*, **33**, 134 (1930) [*C. A.*, **24**, 3806 (1930)].
[17] Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).
[18] Karrer and Schneider, *Helv. Chim. Acta*, **30**, 859 (1947).
[19] Baxendale, Evans, and Park, *Trans. Faraday Soc.*, **42**, 155 (1946).
[20] Hudlecky, *Chem. Listy*, **45**, 380 (1952) [*C. A.*, **47**, 8012 (1953)].
[21] Pastureau, *Compt. rend.*, **140**, 1592 (1905); *Bull. soc. chim. France*, [4] **5**, 227 (1909).
[22] Bacyer and Villiger, *Ber.*, **33**, 1569 (1900).

When ketones with the carbonyl group attached to at least one secondary carbon atom are treated with peracids, esters are formed. The secondary grouping rearranges in preference to a primary one. In the series of alicyclic methyl ketones from methyl cyclobutyl ketone to methyl cycloheptyl ketone, oxidation with perbenzoic acid gives yields of acetates ranging from 58 to 78%.[23]
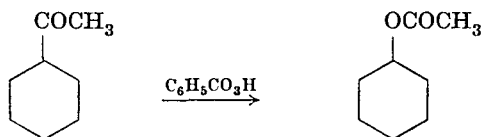
Steroid alcohols with the hydroxyl group attached to C–17 may be prepared conveniently by the Baeyer-Villiger oxidation of 20-keto steroids, such as pregnan-3α,12α-diol-20-one diacetate (VII).
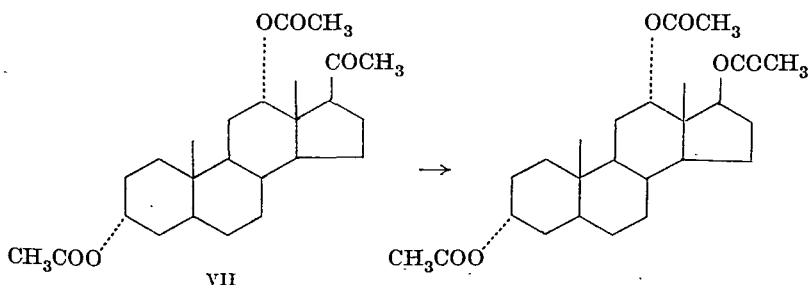
This method was first applied using persulfuric acid,[24] but low yields were sometimes obtained,[25] and alternative procedures for the preparation of C–17 alcohols appeared preferable.[26] However, it has been found that perbenzoic acid and monoperphthalic acid give higher yields, particularly when acid catalysts are present.[27, 28] Also, unlike the alternative procedures, which involve ozonization or nitrosation, the reaction may be applied to unsaturated ketones such as pregnenolone.

The oxidation has been used as the key step in a degradation of sarsapogenin (VIII) to pregnan-3,16,20-triol (IX).[29]

[23] Friess and Pinson, *J. Am. Chem. Soc.*, **74**, 1302 (1952).

[24] Marker and co-workers, *J. Am. Chem. Soc.*, **62**, 650, 2543, 2621, 3003 (1940).

[25] Koechlin and Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

[26] Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., p. 400, Reinhold Publishing Corp., 1949.

[27] Sarett, *J. Am. Chem. Soc.*, **69**, 2899 (1947).

[28] Wieland and Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949).

[29] Marker, Rohrmann, Crooks, Whittle, Jones, and Turner, *J. Am. Chem. Soc.*, **62**, 525 (1940).
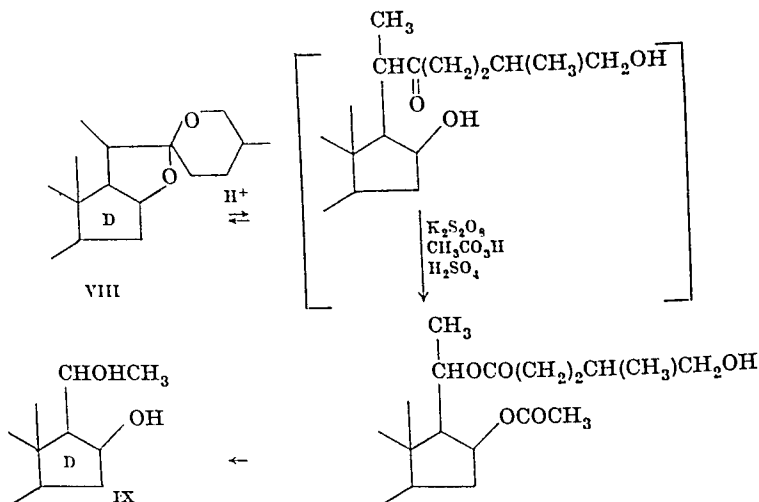
The value of the Baeyer-Villiger reaction in this series is enhanced by decisive evidence that rearrangement occurs with retention of configuration.[7, 30, 31] This fact has been utilized in the preparation of 2-decalols and C–17 hydroxy steroids of definite configuration.[32]

Alicyclic Ketones. Alicyclic ketones ranging from cyclobutanone to cycloheptadecanone (X, $n = 14$)[5, 33, 34] have been oxidized under Baeyer-Villiger conditions. The reaction provides a convenient method for determining structure and for preparing relatively inaccessible lactones and hydroxy acids. When persulfuric acid or hydrogen peroxide-hydrofluoric acid[20] is used for the oxidation, polyesters of the hydroxy acids are obtained. The ethyl esters of the simple hydroxy acids are formed when ethanol is present.[35] Organic peracids give excellent yields of lactones.
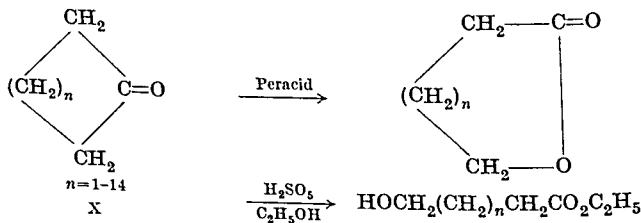
[30] Mislow and Brenner, *J. Am. Chem. Soc.*, **75**, 2319 (1953).

[31] Gallagher and Kritschevsky, *J. Am. Chem. Soc.*, **72**, 882 (1950).

[32] Dauben and Hoerger, *J. Am. Chem. Soc.*, **73**, 1505 (1951).

[33] Friess and Frankenburg, *J. Am. Chem. Soc.*, **74**, 2679 (1952).

[34] Ruzicka and Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

[35] Robinson and Smith, *J. Chem. Soc.*, **1937**, 371.

The oxidation has also been carried out under alkaline conditions but the yields recorded are low.[36-38]

In the steroid series the procedure has been applied to compounds having carbonyl groups at C–3,[28, 39-43] C–7,[44] and C–17.[45, 46] It has been demonstrated that conditions suitable for the oxidation of such compounds do not lead to any action on C–11[27] or C–12[40] carbonyl groups, although oxidation at C–12 does occur when a large excess of peracid is used. There is evidence that oxidation of the C–3 carbonyl group of cholestan-3-one and coprostan-3-one with persulfuric acid is inhibited by the presence of bromine in the 2- or 4-positions,[47] but that is not the case when excess perbenzoic acid is employed.[28] The oxidation of androstan-3-one (XI) gives the lactone XII.[43] 7-Ketocholestan-3β-ol (XIII) is oxidized to the lactone XIV.[44]
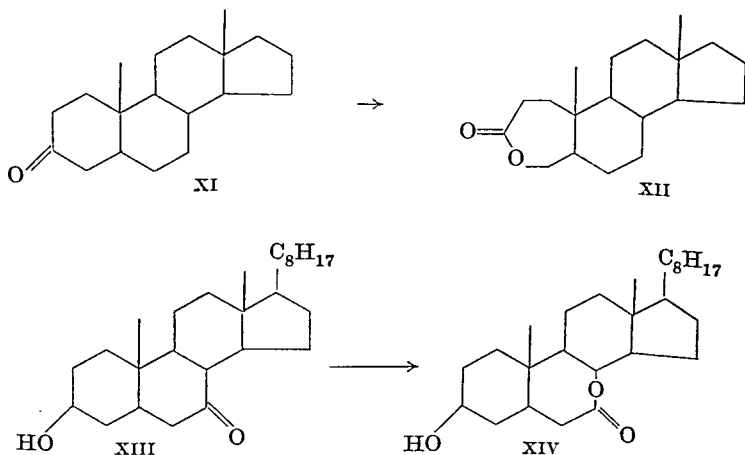
In the oxidation of 17-keto steroids there is some doubt as to which bond adjacent to the carbonyl group is broken, but the evidence available favors the formulation XV for the lactone.[46]

[36] Westerfield, J. Biol. Chem., 143, 177 (1942).

[37] Fling, Minard, and Fox, J. Am. Chem. Soc., 69, 2467 (1947).

[38] Heine and Jones, J. Am. Chem. Soc., 73, 1361 (1951).

[39] Gardner and Godden, Biochem. J., 7, 588 (1913).

[40] Burckhardt and Reichstein, Helv. Chim. Acta, 25, 1434 (1942).

[41] Ruzicka, Prelog, and Meister, Helv. Chim. Acta, 28, 1651 (1945).

[42] Salamon, Z. physiol. Chem., 272, 61 (1941).

[43] Prelog, Ruzicka, Meister, and Wieland, Helv. Chim. Acta, 28, 618, 1651 (1945).

[44] Heusser, Segrè, and Plattner, Helv. Chim. Acta, 31, 1183 (1948).

[45] Jacobsen, J. Biol. Chem., 171, 61 (1947).

[46] Picha, J. Am. Chem. Soc., 74, 703 (1952).

[47] Marker, J. Am. Chem. Soc., 62, 2543 (1940).
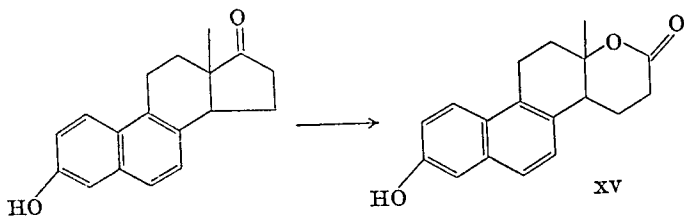
Aromatic Ketones. The oxidation of diaryl ketones with peracids regularly leads to the formation of esters or their hydrolysis products. Although this reaction is of little value as a preparative procedure, it does provide a convenient means of establishing the structures of polysubstituted benzophenones and alkyl aryl ketones.[48] The method is less drastic and more specific than the degradation procedures involving alkali fusion[49] or acid hydrolysis[50] that have been applied to natural products.

In the cleavage of unsymmetrical ketones the migrating group is normally the more electron-releasing one. Substituents in the aromatic nuclei influence the course of reaction in a manner similar to that observed in normal nucleophilic aromatic substitution. Thus treatment of p-methoxybenzophenone with peracetic acid gives benzoic acid and hydroquinone monomethyl ether, while cleavage of p-nitrobenzophenone gives p-nitrobenzoic acid and phenol exclusively.[4]
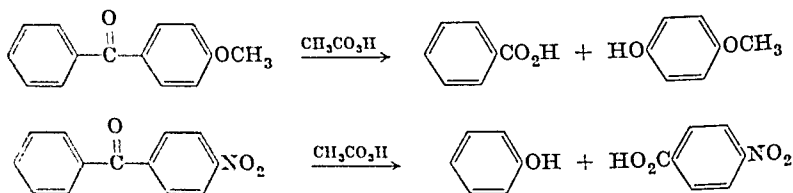
Insufficient information is available to make it possible to predict the course of reaction of alkyl aryl ketones with certainty. Treatment with peracids and hydrogen peroxide in acid or neutral solution may lead to the migration of either the aromatic or the aliphatic group.[10] Thus, with peracetic acid, acetophenone gives a mixture of esters,[4] and cyclohexyl phenyl ketone gives esters XVI and XVII in the approximate proportion of 5 : 1.[51]

$$C_6H_5COC_6H_{11} \rightarrow \underset{XVI}{C_6H_5CO_2C_6H_{11}} + \underset{XVII}{C_6H_{11}CO_2C_6H_5}$$
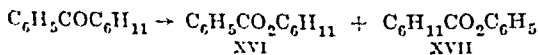
However, in one study of the oxidation of *meta-* and *para*-substituted acetophenones with perbenzoic acid, acetates alone were obtained in good yields.[10]

Alkyl aryl ketones containing hydroxyl groups in the *ortho* or *para* position are converted to polyhydric phenols by hydrogen peroxide in alkaline solution. The yields are poor.[52]

α,β-Unsaturated Ketones. The application of the Baeyer-Villiger reaction to this group of compounds should lead to reaction according to either A or B. Another possibility is preferential attack at the olefinic linkage leading to an α,β-epoxyketone (C).

$$RCH=CHOCOR' \quad \text{A (cleavage toward } C=C)$$

$$RCH=CHCOR' \longrightarrow RCH=CHCO_2R' \quad \text{B (cleavage away from } C=C)$$

$$\overset{O}{RCH-CHCOR'} \quad \text{C}$$
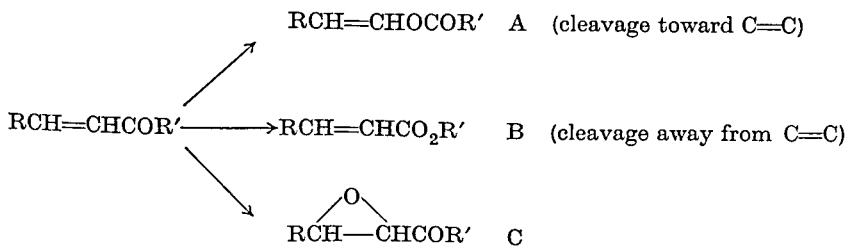
Although only a limited number of cases have been studied, examples of the formation of all three types of compound are available. The oxidation of benzalacetone (XVIII) with peracetic acid leads exclusively to the ester XIX.[53]

$$C_6H_5CH=CHCOCH_3 \quad \rightarrow \quad C_6H_5CH=CHOCOCH_3$$
$$\text{XVIII} \qquad\qquad\qquad \text{XIX}$$
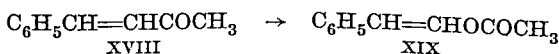
An α-phenyl-α,β-unsaturated ketone (XX) gives a mixture of epoxyketone and the ester XXI.[54]

$$RCH=C(C_6H_5)COCH_3 \rightarrow RCH=C(C_6H_5)CO_2CH_3 + \overset{O}{RCH-C(C_6H_5)COCH_3}$$
$$\text{XX} \qquad\qquad\qquad \text{XXI}$$
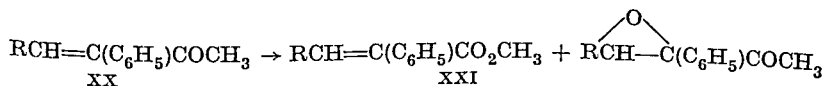
Oxidation of Δ[16]-20-ketosteroids with perbenzoic acid leads to preferential attack at the olefinic linkage. Pregna-5,6-dien-3β-ol-20-one acetate has been converted in this way to 16,17-epoxypregna-5-en-3β-ol-20-one acetate, a useful intermediate in the preparation of 17α-hydroxyprogesterone.[55]

When α,β-unsaturated ketones are treated with hydrogen peroxide in alkaline solution, epoxyketones are formed.[56-58] There is no evidence of the Baeyer-Villiger reaction occurring under these conditions.

[52] Dakin, *Am. Chem. J.*, **42**, 474 (1909).
[53] Böeseken and Soesman, *Rec. trav. chim.*, **52**, 874 (1933).
[54] Wenkert and Rubin, *Nature*, **170**, 708 (1952).
[55] Julian, Meyer, and Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).
[56] Kohler, Richtmeyer, and Hester, *J. Am. Chem. Soc.*, **53**, 213 (1931).
[57] Fieser and co-workers, *J. Am. Chem. Soc.*, **61**, 3216 (1939); **62**, 2866 (1940).
[58] Barkley, Farrar, Knowles, and Raffelson, *J. Am. Chem. Soc.*, **75**, 4110 (1953).

Polycarbonyl Compounds. α-Diketones and α-keto acids react readily with Baeyer-Villiger reagents.[59-64] In inert solvents anhydrides are formed,[65-67] while in alkaline or acidic media simple carboxylic acids are generally produced in good yields. It would appear from some comparisons of conditions that higher yields are obtained when the oxidations are conducted in alkaline solution.[68]

The oxidation has been used in establishing structure and in the preparation of relatively inaccessible carboxylic acids. As typical examples, 9,10-diketostearic acid is converted quantitatively to azelaic and pelargonic acid,[61]

$$CH_3(CH_2)_7COCO(CH_2)_7CO_2H + CH_3CO_3H \rightarrow$$
$$CH_3(CH_2)_7CO_2H + HO_2C(CH_2)_7CO_2H$$
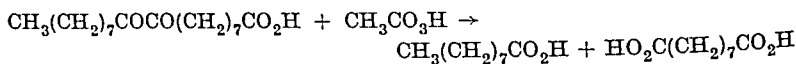
and phenanthraquinone forms diphenic acid.[69, 70]

Unsaturated α-diketones react in a similar manner. Treatment of 4-methyl-*o*-benzoquinone (XXII) with monoperphthalic acid gives β-methylmuconic anhydride XXIII.[65]

XXII   XXIII
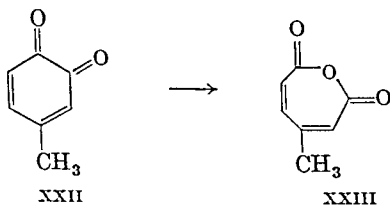
Dicinnamylidenebiacetyl (XXIV) is oxidized to the anhydride XXV,[65]

$$C_6H_5(CH=CH)_2COCO(CH=CH)_2C_6H_5 \rightarrow$$
XXIV

$$C_6H_5(CH=CH)_2CO_2CO(CH=CH)_2C_6H_5$$
XXV
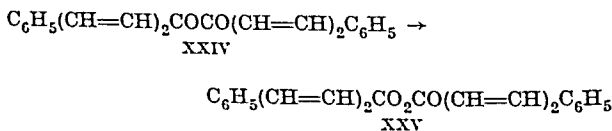
[59] French and Sears, *J. Am. Chem. Soc.*, **70**, 1279 (1948).

[60] Holleman, *Rec. trav. chim.*, **23**, 170 (1904).

[61] Boeseken and Sloof, *Rec. trav. chim.*, **49**, 91 (1930).

[62] Reiswert, *Ber.*, **30**, 1041 (1897).

[63] Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).

[64] Bjorklund and Hatcher, *Trans. Roy. Soc. Can.*, (III), **44**, 25 (1950) [*C. A.*, **45**, 7951 (1951)].

[65] Karrer, Schwyzer, and Neuwirth, *Helv. Chim. Acta*, **31**, 1210 (1948).

[66] Karrer, Cochand, and Neuss, *Helv. Chim. Acta*, **29**, 1836 (1946).

[67] Karrer and Hohl, *Helv. Chim. Acta*, **32**, 1932 (1949).

[68] Meyer, *Helv. Chim. Acta*, **30**, 1976 (1947).

[69] Linstead and Walpole, *J. Chem. Soc.*, **1939**, 855.

[70] Perkin, *Proc. Chem. Soc.*, **23**, 166 (1907).

and puberulic acid (XXVI), presumably reacting through the keto form, is oxidized to aconitic acid (XXVII),[71]

XXVI   XXVII
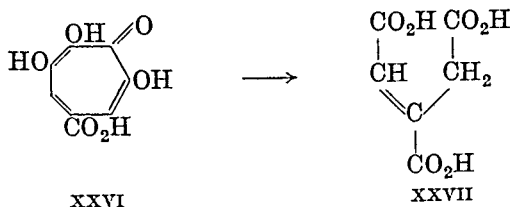
The oxidation of α-diketones normally involves cleavage between the carbonyl groups. However, it has been shown that the reaction of 2,2',4,4'-tetranitrobenzil with alkaline hydrogen peroxide gives 2,4-dinitrophenol and not 2,4-dinitrobenzoic acid which is formed in an acidic medium.[72]

The oxidation of 1,3-diketones and β-keto acids with peracids does not follow the normal pattern of the Baeyer-Villiger reaction. Treatment of dibenzoylmethane derivatives with perbenzoic acid leads to the formation of the corresponding dibenzoylcarbinols.[73-76]

$$C_6H_5COCH_2COC_6H_5 \rightarrow C_6H_5COCH(OH)COC_6H_5$$
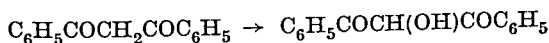
In an earlier study[77] it was found that an equimolecular amount of peracetic acid oxidized 1,3-diketones or β-keto acids to an acid and an alcohol. With excess peracetic acid a mixture of acids is formed. The first reaction was interpreted as involving migration of the group R' lying between the carbonyl groups.

$$RCOCH(R')COR'' + CH_3CO_3H \rightarrow RR'CHOH + R''COCO_2H$$

$$R=CH_3, C_2H_5, C_5H_{11}; \quad R'=H, CH_3, C_6H_5CH_2; \quad R''=CH_3, OC_2H_5$$
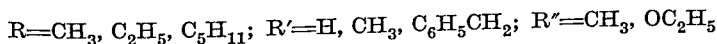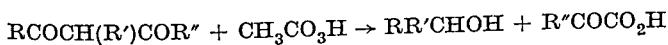
When β-triketones such as 2-acetylindan-1,3-dione (XXVIII) are treated with hydrogen peroxide in diethyl ether there is preferential oxidation of the acyl side chain leading to the formation of an ester (XXIX).[78] In acidic or alkaline media, hydrogen peroxide oxidizes 2-acetylindan-1,3-dione to a mixture of acetic and phthalic acids.

[71] Corbett, Hassall, Johnson, and Todd, *Chemistry & Industry*, 1949, 626.

[72] Blatt and Rytina, *J. Am. Chem. Soc.*, 72, 403 (1950).

[73] Blatt and Hawkins, *J. Am. Chem. Soc.*, 58, 81 (1936).

[74] Karrer, Albers-Schonberg, and Kebrle, *Helv. Chim. Acta*, 35, 1498 (1952).

[75] Karrer, Kebrle, and Thakkar, *Helv. Chim. Acta*, 33, 1711 (1950).

[76] Karrer, Kebrle, and Albers-Schonberg, *Helv. Chim. Acta*, 34, 1014 (1951).

[77] Böeseken and Jacobs, *Rec. trav. chim.*, 55, 804 (1936).

[78] Hassall, *J. Chem. Soc.*, 1948, 50.

$$CH_3(CH_2)_5CHO + H_2O_2 \rightarrow CH_3(CH_2)_5CH(OH)O_2H \xrightarrow{\text{Heat}}$$
$$CH_3(CH_2)_5OCHO + CH_3(CH_2)_5CO_2H$$
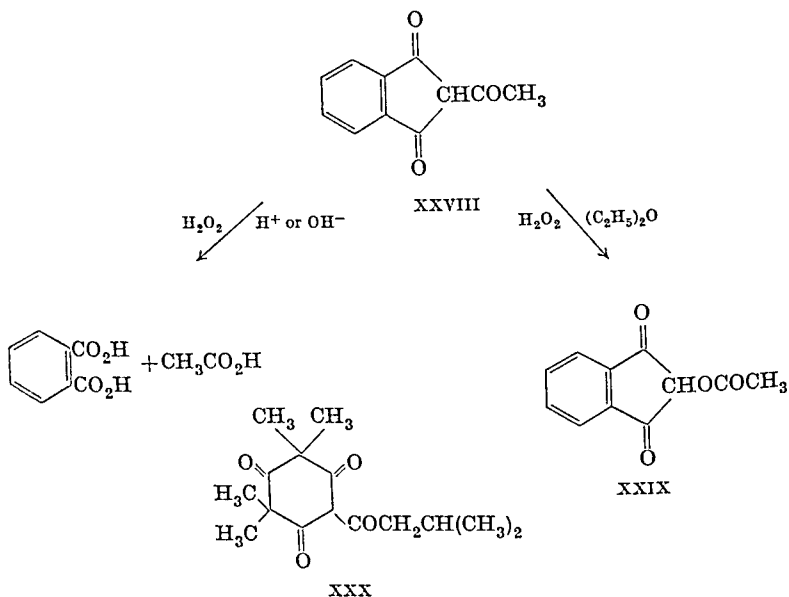
The Baeyer-Villiger reaction has been used in the elucidation of the structure of the natural product leptospermone (XXX).[79]

Aldehydes. Peracids generally convert both aliphatic and aromatic aldehydes to carboxylic acids.[80-83] Hydrogen peroxide reacts with aliphatic aldehydes in neutral media to give hydroxyhydroperoxides.[84, 11] It is significant, however, that such peroxides rearrange readily on heating to give a mixture of the corresponding carboxylic acid and the formate of the next lower alcohol. This behavior suggests that the oxidation of aldehydes with peroxides normally follows the Baeyer-Villiger pattern.
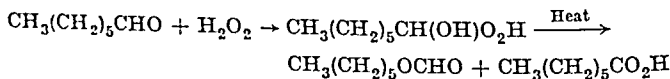
The oxidation of citral (XXXI) to the lower aldehyde XXXII is an example of a similar course of reaction.[85]

[79] Briggs, Hassall, and Short, J. Chem. Soc., 1945, 706.
[80] D'Ans and Kneip, Ber., 48, 1136 (1915).
[81] Wieland and Richter, Ann. 495, 284 (1932).
[82] Lyubarskii and Kagan, J. Phys. Chem., 39, 847 (1935).
[83] Ross, Gebhart, and Gerecht, J. Am. Chem. Soc., 67, 1275 (1945).
[84] Rieche, Alkylperoxyde und Ozonide, p. 36, Steinkopf, Leipzig, 1931.
[85] Prileschajeff, Bull. soc. chim. France, [4] 42, 687 (1927).

$$(CH_3)_2C=CH(CH_2)_2C(CH_3)=CHCHO \xrightarrow{C_6H_5CO_3H}$$

XXXI

$$(CH_3)_2\overset{\displaystyle O}{\overset{\diagup\diagdown}{C}}—CH(CH_2)_2C(CH_3)=CHOCHO \rightarrow$$

$$(CH_3)_2\overset{\displaystyle O}{\overset{\diagup\diagdown}{C}}—CH(CH_2)_2CH(CH_3)CHO + HCO_2H$$

XXXII
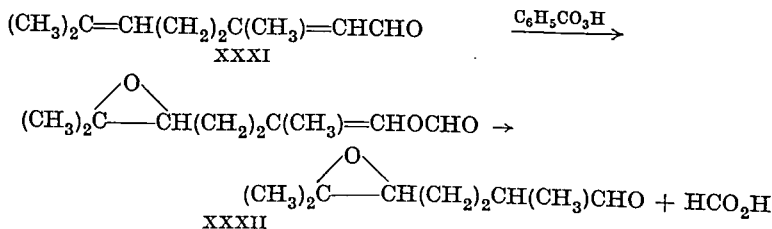
The oxidation of aliphatic aldehydes with hydrogen peroxide in acid and alkaline solution occasionally leads to the formation of hydrogen and hydrocarbons in addition to carboxylic acids.[86-89] Such reactions appear to involve a radical mechanism in addition to the normal ionic process.

Aromatic aldehydes have been oxidized with peroxides in a variety of media. In neutral or acid solution the action of peracids and hydrogen peroxide resembles that with alkyl aryl ketones under similar conditions.[90, 91] Benzaldehyde reacts with hydrogen peroxide in ether to give benzoic acid and only traces of phenol.[92] In aldehydes with electron-releasing substituents such as alkoxyl, hydroxyl, and amino[93] in the *ortho* or *para* positions, the formyl group tends to migrate, producing formates or phenols according to the conditions employed.

The oxidation of aromatic aldehydes in alkaline solution was first studied by Dakin,[52] who indicated that the reaction occurred only when hydroxyl groups were present in the *ortho* or *para* positions. In such cases good yields of polyhydric phenols are obtained through the replacement of formyl by hydroxyl groupings. As Table VI indicates, the Dakin procedure has been applied successfully to a variety of substituted phenolic aldehydes. It has been used for the synthesis of phenols such as morphol[94] (XXIII) which are not readily accessible by other means.

HO   OH   XXXIII
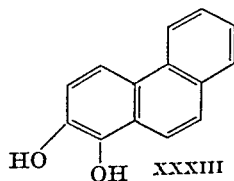
[86] Payne and Lemon, *J. Am. Chem. Soc.*, **63**, 226 (1941).

[87] Fry and Payne, *J. Am. Chem. Soc.*, **53**, 1973 (1931).

[88] Bezzi, *Gazz. chim. ital.*, **63**, 345 (1933).

[89] Bach and Generosov, *Ber.*, **55**, 3560 (1922).

[90] Böeseken and Greup, *Rec. trav. chim.*, **58**, 528 (1939).

[91] Wacek and Bezard, *Ber.*, **74**, 845 (1941).

[92] Späth, Pailer, and Gergeley, *Ber.*, **73**, 935 (1940).

[93] Bamberger, *Ber.*, **36**, 2042 (1903).

[94] Barger, *J. Chem. Soc.*, **113**, 218 (1918).

It is of interest that the aldehydes XXXIV and XXXV, in which there is a nitro group *ortho* to the hydroxyl, are not attacked, while the aldehydes XXXVI and XXXVII react in the normal way.[52] The inhibiting effect
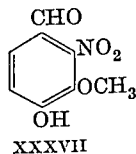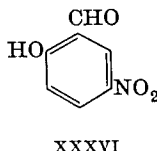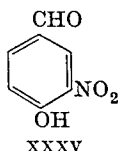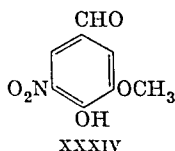
is probably due to intramolecular hydrogen bonding. It has been suggested that the Dakin oxidation follows a different course from the Baeyer-Villiger reaction,[95] but this has not been substantiated.[91]

Side Reactions. Structural elements other than carbonyl groups may be attacked under the conditions used for the Baeyer-Villiger reaction. The susceptibility of olefinic linkages to oxidation by peracids is well known.[96] Aromatic hydrocarbons, such as mesitylene,[97] methylcholanthrene, and benzpyrene,[98] which are particularly sensitive to attack by electrophilic reagents, may be oxidized preferentially. The reactivity of other groupings was reviewed in 1949.[99]

There are some isolated examples of oxidation of the normal products of reaction by Baeyer-Villiger reagents. For example, phenols may react with peracids,[100-102] and demethylation of aromatic ethers may occur.[102] Catechols and hydroquinones may be oxidized through quinones[70] to carboxylic acids.[103, 104] However, if a large excess of reagent is avoided it is generally possible to obtain substantial yields of phenols from Baeyer-Villiger reactions.[48] In one example of the Dakin reaction, the oxidation of 2-hydroxy-5-methoxybenzaldehyde, the formation of an unidentified, abnormal product has been reported.[105]

There is evidence, in two cases, of oxidation of secondary alcohols by the action of excess peracetic acid. When 1,3-diketones react with excess of this peracid, a ketone is obtained in the place of the secondary alcohol produced with an equimolar amount.[77] The steroid hydroxy ketone

[52] Wacek and Eppinger, *Ber.*, 73, 644 (1940).
[94] Swern, *Org. Reactions*, 7, 378 (1953).
[97] Friess and Miller, *J. Am. Chem. Soc.*, 72, 2611 (1950).
[98] Eckhardt, *Ber.*, 73, 13 (1940).
[99] Swern, *Chem. Revs.*, 45, 1 (1949).
[100] Boeseken and Engelberts, *Proc. Acad. Sci. Amsterdam*, 34, 1292 (1931) [*C. A.*, 26, 2970 (1932)].
[101] Fernholz, *Chem. Ber.*, 84, 110 (1951).
[102] Friess, Soloway, Morse, and Ingersoll, *J. Am. Chem. Soc.*, 74, 1305 (1952).
[103] Wacek and Fiedler, *Monatsh.*, 80, 170 (1949).
[104] Weitz, Schobbert, and Seibert, *Ber.*, 68, 1163 (1935).
[105] Rosenblatt and Rosenthal, *J. Am. Chem. Soc.*, 75, 4607 (1953).

XXXVIII is oxidized with excess peracetic acid to the diketone XL and to XLI in addition to the normal product XXXIX.[28] The rearrangement of the double bond from the β,γ to the α,β position resembles that observed in other oxidations of Δ^5-3-hydroxy steroids.[106] The oxidation of *allo*-

pregnan-20-one with persulfuric acid gives, in addition to the normal product androstan-17β-ol, a significant yield of *allo*pregnan-21-ol-20-one.[47] This arises from the action of the peracid on the enolic form of the C–20 keto group.[18]
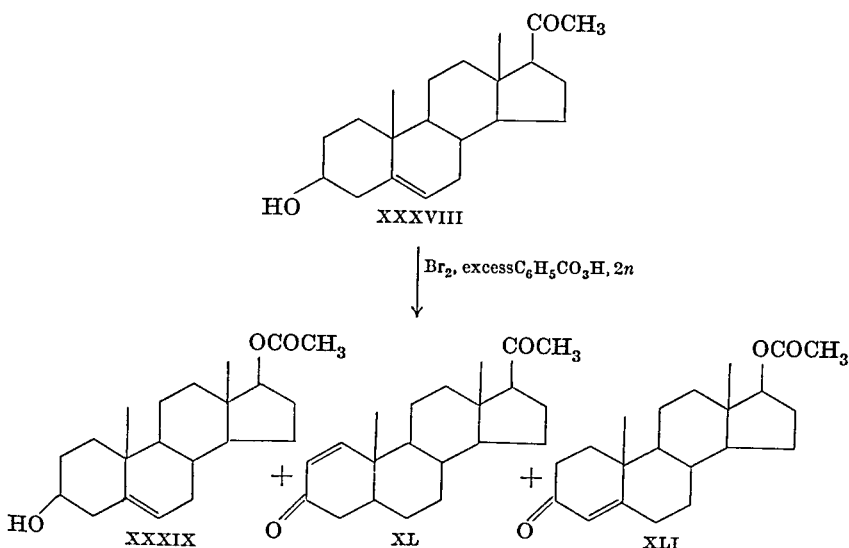
SELECTION OF EXPERIMENTAL CONDITIONS

Peroxides. Hydrogen peroxide, permono- and perdi-sulfuric acid, peracetic acid, perbenzoic acid, and monoperphthalic acid have all been used as reagents in the Baeyer-Villiger reaction. Although there is little precise information on the relative efficiencies of these peroxides, there is sufficient evidence to permit some general conclusions.

Hydrogen peroxide in dilute acid or in neutral solution sometimes converts carbonyl compounds to normal Baeyer-Villiger oxidation products, but more frequently hydroxyhydroperoxides and their condensation products are formed. The simple and condensed peroxides XLII–XLV are produced by the action of hydrogen peroxide in diethyl ether on cyclohexanone.[107, 15] Similar compounds are formed from aliphatic aldehydes[11]

[106] Djerassi, *Org. Reactions*, **6**, 212 (1951).
[107] Milas and Panagiotakos, *J. Am. Chem. Soc.*, **61**, 2430 (1939).

and fluorenone[14] under these conditions, although normal Baeyer-Villiger oxidation products are obtained without difficulty when peracids are used.
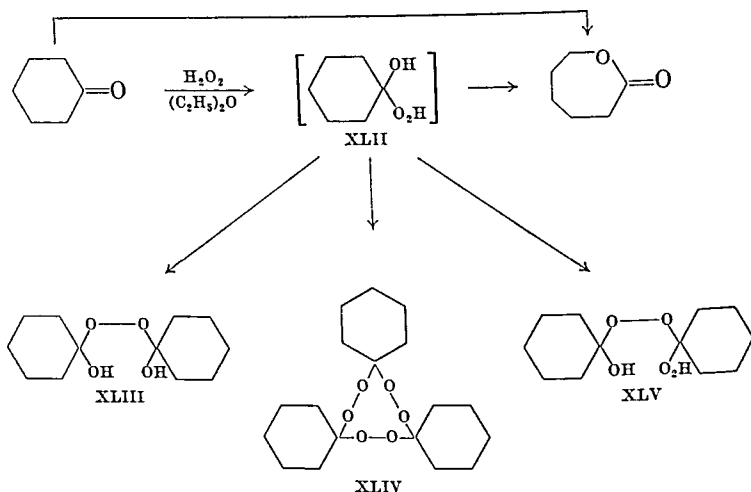
From these observations and the fact that the peroxides of cyclohexanone, fluorenone, and aliphatic aldehydes are converted by heating or by treatment with acids to the Baeyer-Villiger reaction products, it appears that hydrogen peroxide in ether or dilute acid is less effective since it does not favor the dissociation and rearrangement steps postulated for the Baeyer-Villiger reaction (p. 75).

In the related rearrangement of esters of the hydroperoxide formed from decahydronaphthalene (XLVI),[2] the dissociation step is influenced both by hydrogen-ion catalysis and by the nature of the acyl group RCO. The
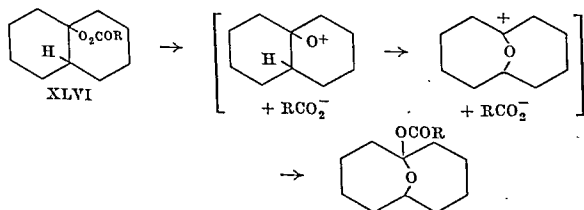
acetate and benzoate rearrange readily on warming. The *p*-nitrobenzoate rearranges more readily than the benzoate, and all attempts to prepare the trichloracetate lead to the rearrangement product. By analogy, it may be expected that the Baeyer-Villiger reaction is favored by conditions leading to the formation of peroxide esters of relatively strong acids. There is little evidence on this point, but the fact that the organic peracids

have proved more generally useful than hydrogen peroxide is in agreement with this view. The more limited applicability of the persulfuric acids is to be attributed in part to the fact that their use in aqueous solution favors the formation of peroxides. Though persulfuric acids and their salts have been used successfully in non-aqueous media, organic peracids are more convenient.

Hydrogen peroxide in alkaline solution differs in reactivity from other Baeyer-Villiger reagents. In the Dakin reaction and the cleavage of α-diketones, alkaline conditions are to be preferred. With α,β-unsaturated ketones, however, these conditions lead exclusively to epoxyketones rather than Baeyer-Villiger reaction products. There has been a useful study of the kinetic course of the oxidation of mesityl oxide and of ethylideneacetone by hydrogen peroxide in an alkaline medium.[107a] It would be desirable to obtain further information on the course and kinetics of reactions involving alkaline hydrogen peroxide.

In all peroxide oxidations of new compounds the possibility of reactions occurring with explosive violence must be considered. Trial experiments should be carried out using small quantities of material. Large excesses of reagents should be avoided, and if significant quantities of unconsumed peroxides remain at the end of the reaction they should be destroyed by reducing agents such as sodium bisulfite or ferrous sulfate before isolation of the products is attempted.

It is generally possible to follow the course of the Baeyer-Villiger reaction by estimating the active oxygen at intervals. Blank determinations should be carried out, particularly when long reaction times are involved, as the reagents may decompose under the conditions of the experiment. Information on conditions influencing the stability of peroxides is included in reviews on the general properties of hydrogen peroxide[108–110] and peracids.[99] In addition to temperature and pH, such factors as intensity of illumination, solvent polarity, and trace-metal impurities may play an important role.[111–113]

The following procedures are convenient for the preparation of the peroxides used in the Baeyer-Villiger reaction. Further information on methods of preparation of organic peracids is included in reviews,[96,99,114] and also procedures for the analysis of peroxides have been summarized.[115]

[107a] Bunton and Minkoff, *J. Chem. Soc.*, **1949**, 665.

[108] Shanley and Greenspan, *Ind. Eng. Chem.*, **39**, 1536 (1947).

[109] Medard, *Compt. rend.*, **222**, 1491 (1946).

[110] Schumb, *Ind. Eng. Chem.*, **41**, 992 (1949).

[111] Böeseken and Blumberger, *Rec. trav. chim.*, **44**, 90 (1925).

[112] Calderwood and Lane, *J. Phys. Chem.*, **45**, 108 (1941).

[113] Meerwein, Ogait, Prang, and Serini, *J. prakt. Chem.*, **113**, 9 (1926).

[114] Criegee, *Fortschr. chem. Forsch.*, **1**, 508 (1950).

[115] Swern, *Org. Reactions*, **7**, 392 (1953).

Hydrogen Peroxide. In alkaline solution, hydrogen peroxide decomposes relatively rapidly and is particularly sensitive to impurities.[108] These facts must be taken into consideration to ensure that a sufficient excess of reagent is available. The majority of Baeyer-Villiger oxidations involving alkaline hydrogen peroxide employ dilute sodium hydroxide in slight excess of the amount required to keep the reactants and products in solution. Ammonium hydroxide[52] and potassium bicarbonate[68] have also been used, and pyridine has been added in reactions in which the sodium salt of the starting material is relatively insoluble in water.[79, 94]

Hydrogen peroxide in ether is conveniently prepared by shaking 50 g. of 30% hydrogen peroxide with five 100-ml. portions of diethyl ether. The ether extract is dried first with sodium sulfate and then with calcium chloride. It contains approximately 2% hydrogen peroxide. A more concentrated solution (4–6%) may be obtained by evaporation of ether from the dilute solution at room temperature under reduced pressure.[92] The concentration of hydrogen peroxide may be determined iodimetrically. Ceric sulfate is used for the titration of hydrogen peroxide when aldehydes are present.[86, 116]

Hydrogen peroxide has also been used in acetone,[95] in formic acid-chloroform,[117] and in acetic acid.[118] It has been shown in the oxidation of androsterone acetate that a dilute solution of peracetic acid in glacial acetic acid is preferable to hydrogen peroxide in acetic acid.[119]

Persulfuric Acid. Baeyer and Villiger's "dry reagent" is prepared by mixing 10 g. of potassium persulfate with 11 g. of concentrated sulfuric acid in a mortar, adding 30 g. of potassium sulfate, and grinding the mixture to a fine powder.[1] This reagent is stable in the absence of moisture.

Oxidations have been carried out using suspensions of the dry reagent[1] or solutions of persulfuric acid in glacial acetic acid,[47] in concentrated and dilute sulfuric acid, in petroleum ether,[34] and in ethanol-sulfuric acid.[35] Methods for the estimation of permono- and perdi-sulfuric acid have been described.[120, 121]

Perbenzoic Acid. Details of the preparation of this acid are given in *Organic Reactions*.[122] A product of 99.7% purity is prepared by vacuum sublimation of crude material at 40°.[123]

[116] Willard and Young, *J. Am. Chem. Soc.*, **55**, 3260 (1933).

[117] Prelog and Kocor, *Helv. Chim. Acta*, **31**, 237 (1948).

[118] Mannich, *Ber.*, **74**, 1007 (1941).

[119] Levy and Jacobsen, *J. Biol. Chem.*, **171**, 71 (1947).

[120] D'Ans and Friederich, *Ber.*, **43**, 1880 (1910).

[121] Rius and Zulueta, *Anales real soc. españ. fis. y quim.*, **44B**, 923 (1948) [*C. A.*, **43**, 2121 (1949)].

[122] Swern, *Org. Reactions*, **7**, 394 (1953).

[123] D'Ans, Mattner, and Busse, *Angew. Chem.*, **65**, 57 (1953).

a typical example, benzophenone is oxidized by peracetic acid in glacial acetic acid to phenyl acetate in 44% yield in one hundred and ninety-two hours, but when concentrated sulfuric acid (25%) is added 82% conversion occurs in thirty minutes.[4]

The oxidation of carbonyl compounds with peroxides in the presence of metal catalysts[132, 133] does not appear to follow the same course as the Baeyer-Villiger reaction.

Temperature and Time. A wide range of temperatures has been employed in Baeyer-Villiger oxidations. In some earlier applications of the reaction the carbonyl compounds were heated under reflux with peroxides in relatively high-boiling solvents. This is not to be recommended as a general procedure. Temperatures above 45° normally lead to excessive decomposition of peroxides, and under such conditions a large excess of reagent is required to replace the loss and may lead to oxidation of the normal products. There are exceptional cases involving the oxidation of aromatic aldehydes and ketones in which higher reaction temperatures have been used successfully, but in these oxidations short reaction times are involved.[48, 94] The reaction is normally carried out at a temperature of 10–40°. Lower temperatures may lead to excessively long reaction times and to reduced yields.[35]

When oxidations are carried out with organic peracids or hydrogen peroxide in neutral media, reaction times may vary from several hours to several weeks, according to the molecular species. As a typical example, oxidation of 3-ketosteroids with perbenzoic acid in chloroform is complete in sixteen hours at 16°, although under the same conditions 20-ketosteroids require seven to ten days for cleavage.[27]

In general, relatively short reaction times are required when oxidations are carried out in alkaline or strongly acidic media.

EXPERIMENTAL PROCEDURES

The following examples illustrate typical procedures for the Baeyer-Villiger reaction.

Catechol (Dakin modification using hydrogen peroxide and sodium hydroxide solution). Detailed directions for the preparation of catechol from salicylaldehyde (69–73%)[134] and for a similar preparation of 3-methoxycatechol[135] are given in *Organic Syntheses*.

3,4-Dihydroxyphenanthrene (Dakin modification using alkaline hydrogen peroxide and pyridine).[94] A solution of 1.11 g. of 3-hydroxy-4-formylphenanthrene (5 millimoles) in 10 ml. of pyridine is placed in a

[132] Treibs, *Ber.*, 72, 1194 (1939).

[133] Milas, *J. Am. Chem. Soc.*, 59, 2342 (1937).

[134] Dakin, *Org. Syntheses, Coll. Vol.* 1, 149, 2nd ed., 1941.

[135] Surrey, *Org. Syntheses*, 26, 90 (1946).

25-ml. flask equipped with a dropping funnel and an exit tube. After the air has been displaced with hydrogen, 0.55 ml. of 30.8% hydrogen peroxide (50 millimoles) and 0.45 ml. of 12.5 N potassium hydroxide (5.6 millimoles) are added. The addition of potassium hydroxide causes a considerable rise in temperature. The solution is allowed to boil for a few seconds. It is then cooled, acidified with excess hydrochloric acid, and extracted with diethyl ether. The ether solution is washed with dilute hydrochloric acid to remove pyridine, dried, and evaporated. The crude residue (1.05 g.) is recrystallized from benzene and petroleum ether to yield 0.83 g. (80%) of pure 3,4-dihydroxyphenanthrene, m.p. 142–3°.

Phenyl p-Nitrobenzoate (Oxidation of a diaryl ketone using peracetic acid with sulfuric acid as catalyst).[4]   A solution of 4.54 g. of p-nitrobenzophenone (20 millimoles) in a mixture of 50 ml. of glacial acetic acid and 30 ml. of concentrated sulfuric acid is treated with external cooling with 8 ml. of 40% peracetic acid (40 millimoles). After thirty minutes at room temperature the mixture is neutralized with sodium carbonate solution and extracted with diethyl ether. The dried ether extract yields on evaporation 4.6 g. (95%) of phenyl p-nitrobenzoate, m.p. 128–130°.

Etiocholan-3α,12α,17β-triol (Oxidation of a 20-keto steroid using perbenzoic acid with sulfuric acid as catalyst).[28]   Ninety grams of 3α,12α-diacetoxypregnan-20-one (0.22 mole) and 44 ml. of a 10% solution of sulfuric acid in glacial acetic acid are added separately with external cooling to 440 ml. of a chloroform solution containing 68.6 g. (0.49 mole) of perbenzoic acid. The solution is allowed to stand in the dark at room temperature for ten days. After dilution with diethyl ether, the mixture is washed in turn with water, dilute sodium carbonate solution, and water. The organic layer is dried, and the solvent is evaporated. The residue is saponified by boiling for one hour with a solution of 60 g. of sodium hydroxide in 850 ml. of methanol and 50 ml. of water. After much of the methanol has been removed by distillation under reduced pressure, sufficient ether is added to keep the product in solution. The ether solution is washed with water until neutral, dried, concentrated to 600 ml., and cooled to —10° to precipitate 46.3 g. of etiocholan-3α,12α,17β-triol, m.p. 231–232°. Treatment of the concentrated mother liquor with Girard's Reagent P furnishes an additional 0.73 g. of the triol and 6.17 g. of starting material. The total yield of triol is 71%.

Diphenic Acid (Cleavage of an α-diketone using alkaline hydrogen peroxide).[136]   A suspension of 1 g. of 9,10-phenanthraquinone (4.8 millimoles) in 20 ml. of 5% aqueous sodium hydroxide is mixed with 2.5 ml. of 27% hydrogen peroxide (19 millimoles) and allowed to stand with

---

[136] C. H. Hassall, unpublished observations.

occasional stirring at 30°. Further additions of 2.5 ml. of 27% hydrogen peroxide are made after six hours and again after an additional twelve hours. After a total of forty-eight hours the mixture is filtered from a trace of insoluble material and acidified. The precipitate of pure diphenic acid formed is collected on a filter, washed with water, and dried; the yield is 1.09 g. (94%), m.p., 229–230°.*

2-Acetoxyindan-1,3-dione (Selective oxidation of a triketomethane derivative using hydrogen peroxide in ether).[78] A solution containing 1 g. of 2-acetylindan-1,3-dione (5.3 millimoles) in 80 ml. of diethyl ether is treated with 12 ml. (18 millimoles) of 5% hydrogen peroxide in ether and allowed to stand in a closed flask at 15°. After twenty-one days the ether is evaporated. The residue is triturated with 3 ml. of water, filtered, and extracted with chloroform. The chloroform extract is filtered from a trace of phthalic acid and evaporated. The residue is crystallized twice from ethyl acetate-petroleum ether (40–60°) to give 0.70 g. (64%) of 2-acetoxyindan-1,3-dione, m.p. 96°.

Lactone $C_{21}H_{32}O_4$ from Isoandrosterone Acetate (Oxidation of a 17-keto steroid using peracetic acid with p-toluenesulfonic acid as catalyst).[119] A solution of 0.274 g. of isoandrosterone acetate (0.83 millimole) in 2 ml. of glacial acetic acid, 5 ml. of 9.5% peracetic acid in acetic acid (6.75 millimoles), and 25 mg. of p-toluenesulfonic acid are mixed and allowed to stand for twenty-three hours at 35° in the dark. The mixture is then treated with a large excess of water which precipitates 0.252 g. (88%) of the crude lactone, m.p. 156–158.5°. This product is converted by one crystallization from benzene-neohexane to the pure lactone, $C_{21}H_{32}O_4$, m.p. 158–159.5°.

TABLE I

BAEYER-VILLIGER OXIDATION OF SATURATED ALIPHATIC KETONES

	Carbonyl Compound	Reagent*	Product	Yield, %	Reference
C_3H_6O	Acetone	H_2SO_5	Acetone peroxide	65	138, 139, 140, 64
	Acetone	H_2O_2, H_2SO_4	Acetone peroxide, hydroxyacetone	—	21
C_4H_8O	Butanone	H_2O_2, H_2SO_4	Butanone peroxide, 3-hydroxybutanone	—	21, 140
C_5H_8O	Acetylcyclopropane	$C_6H_5CO_3H$	No reaction	—	141, 140
$C_5H_{10}O$	3-Pentanone	H_2O_2, H_2SO_4	3-Pentanone peroxide, 2-hydroxypentan-3-one	—	21
$C_6H_{10}O$	Acetylcyclobutane	$C_6H_5CO_3H$	Cyclobutyl acetate	58	23
$C_7H_{12}O$	Acetylcyclopentane	$C_6H_5CO_3H$	Cyclopentyl acetate	61	23
$C_8H_{14}O$	cis-1-Acetyl-2-methylcyclopentane	$C_6H_5CO_3H$	cis-2-Methylcyclopentyl acetate	66	7
	trans-1-Acetyl-2-methylcyclopentane	$C_6H_5CO_3H$	trans-2-Methylcyclopentyl acetate	64	7
	Acetylcyclohexane	$C_6H_5CO_3H$	Cyclohexyl acetate	67	141, 23
$C_8H_{16}O$	2-Octanone	H_2O_2, HF	n-Hexyl acetate	51	20
$C_9H_{16}O$	cis-1-Acetyl-2-methylcyclohexane	$C_6H_5CO_3H$	cis-2-Methylcyclohexyl acetate	63	7
	trans-1-Acetyl-2-methylcyclohexane	$C_6H_5CO_3H$	trans-2-Methylcyclohexyl acetate	55	7
	Acetylcycloheptane	$C_6H_5CO_3H$	Cycloheptyl acetate	69	23
$C_{10}H_{12}O$	3-Phenylbutan-2-one	$C_6H_5CO_3H$	Phenylmethylcarbinyl acetate	87	30
$C_{12}H_{20}O$	cis-cis-Acetyldecahydronaphthalene	$C_6H_5CO_3H$	cis-cis-Decahydro-2-naphthol	65	32
$C_{21}H_{34}O$	Allopregnan-20-one	$K_2S_2O_8$, CH_3CO_2H, H_2SO_4	Allopregnan-21-ol-21-one acetate, androstan-17β-ol†	30–35	47
$C_{21}H_{32}O_2$	Δ⁵-Pregnen-3β-ol-20-one	$C_6H_5CO_3H$	Testosterone acetate, progesterone, Δ⁵-androsten-3β,17β-diol 17-monoacetate	—	28
$C_{23}H_{34}O_3$	Δ⁵-Pregnen-3β-ol-20-one acetate	Monoperphthalic acid, CHCl₃‡	Δ⁵-Androsten-3β,17β-diol	63	28, 47
	Δ⁵-Pregnen-3β-ol-20-one acetate	$C_6H_5CO_3H$, CHCl₃, H_2SO_4	Δ⁵-Androsten-3β,17β-diol	60	28
$C_{23}H_{34}O_4$	Pregnan-3α-ol-11,20-dione acetate	$C_6H_5CO_3H$	Etiocholan-3α,17β-diol-11-one diacetate†	85	27
$C_{23}H_{36}O_3$	Allopregnan-3β-ol-20-one acetate	$C_6H_5CO_3H$	Androstan-3β,17β-diol†	3	40
	Allopregnan-3α-ol-20-one acetate	$K_2S_2O_8$, CH_3CO_2H, H_2SO_4	Androstan-3α,17β-diol diacetate†	—	142
	Pregnan-3α-ol-20-one acetate	$C_6H_5CO_3H$	Androstan-3α,17β-diol diacetate†	52	31, 47
	17-Isopregnan-3α-ol-20-one acetate	$C_6H_5CO_3H$	Etiocholan-3α,17α-diol diacetate	53	31
$C_{25}H_{38}O_5$	Pregnan-3α,12α-diol-20-one diacetate	$C_6H_5CO_3H$, CHCl₃, H_2SO_4§	Etiocholan-3α,12α,17β-triol	77	28, 27
$C_{25}H_{36}O_4$	Pregnan-3α-ol-11,20-dione benzoate	$C_6H_5CO_3H$	Etiocholan-3α,17β-diol-11-one 3-benzoate 17-acetate†	18	27

Note: References 138–164 are listed on p. 106.

* Where CH_3CO_2H is indicated, acetic acid is always present; where H_2SO_4 is shown, sulfuric acid is present; where $C_6H_5CO_3H$ is shown, chloroform is present.

† The configuration at C-17 assigned by the author has been changed. The correction follows from the unequivocal evidence, only available after the completion of the investigation, that the Baeyer-Villiger reaction occurs with retention of configuration.

‡ A catalytic amount of p-$CH_3C_6H_4SO_3H$ was added.

§ Catalytic amount.

TABLE II

BAEYER-VILLIGER OXIDATION OF ALICYCLIC KETONES

	Carbonyl Compound	Reagent*	Product	Yield, %	Reference
C_4H_6O	Cyclobutanone	$C_6H_5CO_3H$	Butyrolactone	70	33
C_5H_8O	Cyclopentanone	H_2O_2, NaOH	5-Hydroxyvaleric acid lactone	18	37, 36
		H_2O_2, HF	Polyesters of 5-hydroxyvaleric acid	86–89	20
		$K_2S_2O_8$, H_2SO_4, C_2H_5OH	Ethyl 5-hydroxyvalerate	70	113, 35
		$C_6H_5CO_3H$	5-Hydroxyvaleric acid lactone	78	5
		H_2O_2, HNO_3	Cyclopentanone peroxide		64
		H_2O_2, HF	6-Hydroxycaproic acid lactone, polyesters of 6-hydroxycaproic acid	8, 81	20
$C_6H_{10}O$	Cyclohexanone	H_2SO_5	Polyesters of 6-hydroxycaproic acid		110, 69
		$K_2S_2O_8$, H_2SO_4, C_2H_5OH	Ethyl 6-hydroxycaproate	39–15	35
		H_2O_2, NaOH	6-Hydroxycaproic acid	19	38
		$C_6H_5CO_3H$	6-Hydroxycaproic acid lactone	71	5, 111
$C_7H_{12}O$	3-Methylcyclohexanone		3-Methylcyclohexanone peroxide		133
	Cycloheptanone	$K_2S_2O_8$, H_2SO_4	Ethyl 7-hydroxyheptanoate	47	35, 133
		$C_6H_5CO_3H$	7-Hydroxyenanthic acid lactone	97	5
$C_8H_{14}O$	Cyclooctanone	$C_6H_5CO_3H$	8-Hydroxycaprylic acid lactone	61	33
$C_{10}H_{10}O$	α-Tetralone	H_2SO_5	1-Hydroxy-1-(o-hydroxyphenyl)-butyric acid lactone		115
$C_{10}H_{16}O$	Camphor	H_2SO_5	Campholide	22	1
$C_{10}H_{18}O$	p-Menthan-2-one	H_2SO_5	6-Hydroxy-3-isopropylenanthic acid lactone	10	1
	Menthone	H_2SO_5	6-Hydroxy-3,7-dimethylcaprylic acid lactone	82	110, 133
$C_{13}H_{24}O$	Cyclotridecanone	H_2SO_5	13-Hydroxytridecanoic acid lactone	11	34
$C_{14}H_{26}O$	Cyclotetradecanone	H_2SO_5	14-Hydroxymyristic acid lactone	35	34
$C_{15}H_{28}O$	Cyclopentadecanone (Exaltone)	H_2O_2, H_2SO_4, CH_3CO_2H	15-Hydroxypentadecanoic acid lactone	17	31
		H_2O_2, H_2SO_4	Cyclopentadecanone peroxide, 15-hydroxypentadecanoic acid lactone		146
$C_{16}H_{30}O$	Cyclohexadecanone	H_2SO_5	16-Hydroxypalmitic acid lactone	30	34
$C_{17}H_{32}O$	Cycloheptadecanone	H_2SO_5	17-Hydroxymargaric acid lactone	65	31

$C_{18}H_{22}O_2$	Estrone	H_2O_2, NaOH	Lactone $C_{18}H_{22}O_3$	42	36
$C_{19}H_{30}O$	Androstan-3-one	$C_6H_5CO_3H$	Lactone $C_{19}H_{30}O_2$	10	43
$C_{19}H_{30}O_2$	Androstan-3-one-17β-ol	$C_6H_5CO_3H$	Lactone $C_{19}H_{30}O_3$	32	43
$C_{20}H_{30}O_3$	Equilenin acetate	CH_3CO_3H†	Acetate of lactone $C_{18}H_{18}O_3$	55	147
	(±)-Isoequilenin acetate	CH_3CO_3H†	Acetate of lactone $C_{18}H_{18}O_3$	69	46
$C_{20}H_{24}O_3$	Estrone acetate	H_2O_2, CH_3CO_2H	Acetate of lactone $C_{18}H_{22}O_3$	57–63	45
$C_{21}H_{30}O_2$	Δ⁵-Pregnen-3β-ol-20-one	$Br_2 \rightarrow C_6H_5CO_3H \rightarrow Zn$	Lactone $C_{21}H_{30}O_3$	—	63
$C_{21}H_{30}O_3$	Androsterone acetate	CH_3CO_3H†	Acetate of lactone $C_{19}H_{30}O_3$	79	119
	Isoandrosterone acetate	CH_3CO_3H†	Acetate of lactone $C_{19}H_{30}O_3$	89–92	119
$C_{23}H_{33}BrO_4$	4-Bromo-12α-acetoxypregnan-3,20-dione	$C_6H_5CO_3H \rightarrow$ pyridine	Lactone $C_{23}H_{32}O_5$, lactone $C_{21}H_{30}O_5$	—	63
$C_{25}H_{38}O_3$	Δ¹¹-3-Ketocholenic acid methyl ester	$C_6H_5CO_3H$	Lactone $C_{25}H_{38}O_5$	68	148
$C_{25}H_{40}O_3$	3-Ketocholanic acid methyl ester	$C_6H_5CO_3H$	Lactone $C_{25}H_{40}O_4$	68	40
$C_{26}H_{38}O_3$	Etiocholan-17β-ol-3-one benzoate	$C_6H_5CO_3H$	Lactone $C_{26}H_{38}O_4$	95	41
$C_{27}H_{42}O_5$	3-Keto-12β-acetoxycholanic acid methyl ester	$C_6H_5CO_3H$	Lactone $C_{27}H_{42}O_6$	—	40
$C_{27}H_{44}O_2$	Cholestandlone	$(NH_4)_2S_2O_8$, H_2SO_4	Lactone $C_{27}H_{44}O_4$ (?)	46	149
$C_{27}H_{46}O$	Coprostan-3-one	$C_6H_5CO_3H$	Lactone $C_{27}H_{46}O_2$	80	40, 39
	Cholestan-3-one	$C_6H_5CO_3H$	Lactone $C_{27}H_{46}O_2$	59	40
$C_{27}H_{46}O_2$	7-Ketocholestan-3β-ol	$C_6H_5CO_3H$	Lactone $C_{27}H_{46}O_3$	87	44
$C_{29}H_{48}O_3$	7-Ketocholestan-3β-ol acetate (benzoate or pivalate)	$C_6H_5CO_3H$	Derivatives of lactone $C_{27}H_{46}O_3$	86–100	44

Note: References 138–164 are listed on p. 106.

* Where CH_3CO_2H is indicated, acetic acid is always present; where H_2SO_4 is shown, sulfuric acid is present; where $C_6H_5CO_3H$ is shown, chloroform is present.

† A catalytic amount of p-$CH_3C_6H_4SO_3H$ was added.

TABLE III

BAEYER-VILLIGER OXIDATION OF ALIPHATIC AROMATIC, ALICYCLIC AROMATIC, AROMATIC, AND HETEROCYCLIC KETONES

	Carbonyl Compound	Reagent	Product	Yield, %	Reference
C_8H_7ClO	p-Chloroacetophenone	$C_6H_5CO_3H$	p-Chlorophenyl acetate	57	10
C_8H_8O	Acetophenone	CH_3CO_3H	Phenyl acetate	33	48, 4
		$C_6H_5CO_3H$	Phenyl acetate	63	111
$C_8H_8O_2$	o-Hydroxyacetophenone	H_2O_2, NH_3	Catechol	10–50	52
	m-Hydroxyacetophenone	H_2O_2, NH_3	No reaction	—	52
	p-Hydroxyacetophenone	H_2O_2, NH_3	Hydroquinone	—	52
$C_8H_8O_3$	2,4-Dihydroxyacetophenone	H_2O_2, NH_3	Hydroxyhydroquinone	—	52
	2,5-Dihydroxyacetophenone	H_2O_2, NH_3	Hydroxyhydroquinone	50	18
$C_9H_7O_2Cl$	2-Methoxy-4-chloroacetophenone	CH_3CO_3H*	4-Methoxy-t-chlorophenyl acetate, 5-chloroguaiacol	Trace	10
$C_9H_{10}O$	p-Methylacetophenone	$C_6H_5CO_3H$	p-Cresyl acetate	73	111
	Propiophenone	$C_6H_5CO_3H$	Phenyl propionate	73	52
$C_9H_{10}O_2$	p-Hydroxypropiophenone	H_2O_2, NH_3	Hydroquinone	—	49
	o-Methoxyacetophenone	CH_3CO_3H	Guaiacol	—	10
	m-Methoxyacetophenone	$C_6H_5CO_3H$	m-Methoxyphenyl acetate	52	10
	p-Methoxyacetophenone	$C_6H_5CO_3H$	p-Methoxyphenyl acetate	66	10, 44, 90, 91
$C_{10}H_{10}O_3$	2-Hydroxy-4-methoxyacetophenone	H_2O_2, NH_3	1,2-Dihydroxy-1-methoxybenzene	—	150
$C_{10}H_{10}O_3$	p-Acetoxyacetophenone	$C_6H_5CO_3H$	Hydroquinone diacetate	90	10
$C_{10}H_{11}NO_2$	p-Acetaminoacetophenone	$C_6H_5CO_3H$	p-Acetaminophenyl acetate	90	71
$C_{10}H_{12}O_3$	2,4-Dimethoxyacetophenone	CH_3CO_3H	2,4-Dimethoxyphenol	—	48
	2,5-Dimethoxyacetophenone	CH_3CO_3H*	2,5-Dimethoxyphenyl acetate	—	49
	2,4-Dihydroxy-3,5-dimethylacetophenone (clavatol)	H_2O_2, NaOH	3-Hydroxy-2,6-dimethylbenzoquinone	30	151

Formula	Compound	Reagent	Product	Yield	Reference
$C_{11}H_{14}O$	Acetomesitylene	$C_6H_5CO_3H$	No product isolated	—	97
$C_{11}H_{14}O_4$	2,4,5-Trimethoxyacetophenone	CH_3CO_3H *	2,4,5-Trimethoxyphenyl acetate	—	48
	2,3,4-Trimethoxyacetophenone	CH_3CO_3H *	2,3,4-Trimethoxyphenyl acetate	—	48
$C_{12}H_{14}O_4$	1,3-Diacetyl-4,6-dimethoxybenzene	CH_3CO_3H *	4,6-Dimethoxyresorcinol diacetate	—	48
$C_{13}H_8O$	Fluorenone	CH_3CO_3H, H_2SO_4	2'-Hydroxybiphenyl-2-carboxylic acid lactone	53	4
		H_2O_2, $(C_2H_5)_2O$	Fluorenone peroxide,	20	14
			2'-Hydroxybiphenyl-2-carboxylic acid lactone	96	
		H_2SO_5, $(CH_3CO)_2O$	2'-Hydroxybiphenyl-2-carboxylic acid lactone	—	14
$C_{13}H_8N_2O_5$	o,p'-Dinitrobenzophenone	CH_3CO_3H, H_2SO_4	No reaction	—	4, 131
	p,p'-Dinitrobenzophenone	CH_3CO_3H, H_2SO_4	p-Nitrophenol, p-nitrobenzoic acid	54, 82	4
$C_{13}H_9BrO$	p-Bromobenzophenone	CH_3CO_3H, H_2SO_4	Phenyl p-bromobenzoate	60	4
$C_{13}H_9ClO$	p-Chlorobenzophenone	CH_3CO_2H, H_2SO_4	Phenyl p-chlorobenzoate, phenol, p-chloro-benzoic acid	77	4
$C_{13}H_9NO_3$	p-Nitrobenzophenone	CH_3CO_3H, H_2SO_4	Phenyl p-nitrobenzoate	95	4, 131
$C_{13}H_{10}O$	Benzophenone	H_2SO_5, $(CH_3CO)_2O$	Phenyl benzoate	Quantitative	140, 4
$C_{13}H_{11}NO$	p-Aminobenzophenone	CH_3CO_3H, $(CH_3CO)_2O$	Phenyl p-aminobenzoate	38	4
$C_{13}H_{16}O$	Phenyl cyclohexyl ketone	CH_3CO_3H	Cyclohexanol, benzoic acid, phenol, hexahydrobenzoic acid	6, 33, 5, 5	4
		$C_6H_5CO_3H$	Cyclohexyl benzoate, phenyl hexahydrobenzoate	71, 15	51
$C_{13}H_{16}O_3$	1,3-Diacetyl-4,5,6-trimethoxybenzene	CH_3CO_3H *	4,5,6-Trimethoxyresorcinol diacetate	—	48
	1,3-Diacetyl-2,4,5-trimethoxybenzene	CH_3CO_3H *	2,4,5-Trimethoxyresorcinol diacetate	—	48
$C_{14}H_{11}NO_2$	3-Phenyldioxindole	H_2O_2, NaOH	o-Aminobenzophenone	14	152
$C_{14}H_{12}O$	p-Methylbenzophenone	CH_3CO_3H	p-Cresyl benzoate	96	4
$C_{14}H_{12}O_2$	p-Methoxybenzophenone	CH_3CO_2H, H_2SO_4	p-Methoxyphenyl benzoate	—	4
$C_{15}H_{13}NO_2$	3-(o-Tolyl)dioxindole	H_2O_2, NaOH	o-Methyl-o'-aminobenzophenone	—	152
	3-(m-Tolyl)dioxindole	H_2O_2, NaOH	m-Toluic acid	—	152
	3-(p-Tolyl)dioxindole	H_2O_2, NaOH	p-Methyl-o'-aminobenzophenone	—	152
$C_{15}H_{13}NO_3$	3-(o-Methoxyphenyl)dioxindole	H_2O_2, NaOH	o-Methoxy-o'-aminobenzophenone	—	152
	3-(m-Methoxyphenyl)dioxindole	H_2O_2, NaOH	m-Toluic acid	—	152
	3-(p-Methoxyphenyl)dioxindole	H_2O_2, NaOH	p-Methoxy-o'-aminobenzophenone	—	152
$C_{16}H_{16}O$	Phenyl mesityl ketone	CH_3CO_3H, H_2SO_4	Benzoic acid	10	4

Note: References 188–454 are listed on p. 354.

* A catalytic amount of $p\text{-}CH_3C_6H_4SO_3H$, H_2SO_4 was added.

TABLE IV

BAEYER-VILLIGER OXIDATION OF α,β-UNSATURATED CARBONYL COMPOUNDS

	Carbonyl Compound	Reagent	Product	Yield, %	Reference
$C_8H_4O_2$	Benzoquinone	H_2O_2, NaOH	cis-Ethylene oxide dicarboxylic acid	53-6	101
$C_9H_{10}O$	Mesityl oxide	H_2O_2, NaOH	1,1-Dimethyl-2-acetylethylene oxide	—	63
$C_{10}H_6O_2$	α-Naphthoquinone	H_2O_2, NaOH	α-Naphthoquinone oxide	38	153, 63
$C_{10}H_{10}O$	Benzalacetone	CH_3CO_3H	Enol acetate of phenylacetaldehyde	70	63, 56, 153
		H_2O_2, NaOH	1-Phenyl-2-acetylethylene oxide	85	85
		$C_6H_5CO_3H$	Enol formate of 2,6-dimethyl-5,6-epoxyheptaldehyde	67	57
$C_{10}H_{10}O$	Citral	H_2O_2, NaOH	2-Methyl-1,4-naphthoquinone oxide	—	77
$C_{11}H_8O_2$	2-Methyl-1,4-naphthoquinone	CH_3CO_3H	2-Methyl benzoyl ketone	68	77
$C_{11}H_{12}O$	Methyl β-methylstyryl ketone	CH_3CO_3H	Enol acetate of methyl benzyl ketone	89	63
	Ethyl styryl ketone	H_2O_2, NaOH	Enol propionate of phenylacetaldehyde	—	58
$C_{15}H_{12}O$	Benzalacetophenone	H_2O_2, NaOH	1-Phenyl-2-benzoylethylene oxide	—	63
$C_{20}H_{24}O_3$	($\pm$)-11-Keto-Δ^{16},21-norprogesterone	H_2O_2, NaOH	($\pm$)-11-Keto-16α,17α-epoxy-21-norprogesterone	43	42, 27
$C_{21}H_{14}O$	10-Benzalanthrone	$K_2S_2O_8$, CH_3CO_2H, H_2SO_4	10,11-Epoxybenzalanthrone	—	63
$C_{21}H_{30}O_2$	Progesterone	H_2O_2, NaOH	Lactone $C_{21}H_{30}O_3$	56	63
$C_{23}H_{19}NO$	2-Dimethylamino-10-benzalanthrone	$C_6H_5CO_3H$	2-Dimethylaminoanthraquinone, benzoic acid	21	148
$C_{23}H_{33}O_3$	Pregna-5,16-dien-3β-ol-20-one acetate	$C_6H_5CO_3H$	16,17-Epoxypregna-5-en-3β-ol-20-one acetate	63	42
$C_{25}H_{36}O_3$	Methyl $\Delta^{4,11,3}$-ketocholadienate	$K_2S_2O_8$, CH_3CO_2H, H_2SO_4	Methyl $\Delta^{4,11,12}$-epoxy-3-ketocholenate		
$C_{27}H_{44}O$	Δ^4-Cholesten-3-one		Lactone $C_{27}H_{44}O_2$		
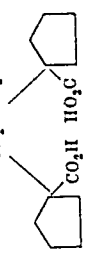
Note: References 138-164 are listed on p. 106.

TABLE V

BAEYER-VILLIGER OXIDATION OF POLYCARBONYL COMPOUNDS

	Carbonyl Compound	Reagent	Product	Yield, %	Reference
			α-Diketones		
$C_4H_6O_2$	Biacetyl	Perphthalic acid	Acetic acid	24	67, 61
$C_5H_8O_3$	Ethyl pyruvate	Perphthalic acid	Monoethyl ester of acetic-carbonic anhydride	—	8
$C_6Br_4O_2$	Tetrabromo-o-benzoquinone	$C_6H_5CO_3H$	2,3,5-Tribromo-4-hydroxymuconolactone	30	17, 154
$C_6Cl_4O_2$	Tetrachloro-o-benzoquinone	Perphthalic acid	2,3,5-Trichloro-4-hydroxymuconolactone, tetrachloromuconic acid	4 31	155
$C_6H_4O_2$	o-Benzoquinone	CH_3CO_3H	cis,cis-Muconic acid	—	61
$C_6H_{10}O_2$	Hexane-3,4-dione	Perphthalic acid	Propionic acid	—	67
$C_7H_6O_2$	p-Methyl-o-benzoquinone	Perphthalic acid	β-Methylmuconic anhydride	22	65
$C_8H_6O_3$	Ethyl phenylglyoxalate	Perphthalic acid	Monoethyl ester of benzoic-carbonic anhydride	—	8
$C_9H_7NO_5$	o-Nitrophenylpyruvic acid	H_2O_2, NaOH	o-Nitrophenylacetic acid	92	62
$C_9H_{12}O_3$	1,2,4-Triketo-3,3,5,5-tetramethylcyclopentane	H_2O_2	Tetramethylacetonedicarboxylic acid	Quantitative	79
$C_{10}H_6O_2$	β-Naphthoquinone	CH_3CO_3H	o-Carboxyallocinnamic acid	70	61
		$C_6H_5CO_3H$	o-Carboxyallocinnamic anhydride	22	17
		CH_3CO_3H	Phthalic acid	—	156
$C_{11}H_8O_3$	6-Methoxy-1,2-naphthoquinone	Perphthalic acid	2-Carboxy-5-methoxycinnamic acid	23	59
		CH_3CO_3H	2-Carboxy-5-methoxycinnamic acid	31	59
$C_{12}H_5BrO_8$	β-Bromolaccain	H_2O_2, CH_3CO_2H	4-Ketocarboxy-2,3,5-tricarboxyphenol (?)	—?	157
$C_{12}H_6O_2$	Acenaphthenequinone	CH_3CO_2H	Naphthalic acid	—	156
$C_{14}H_4N_4O_{10}$	2,2',4,4'-Tetranitrobenzil	H_2O_2, NaOH	2,4-Dinitrophenol	53	72
		H_2O_2, CH_3CO_2H	2,4-Dinitrobenzoic acid		72
$C_{14}H_8O_2$	9,10-Phenanthraquinone	H_2O_2, NaOH	Diphenic acid	Quantitative	136, 150
$C_{14}H_{10}O_2$	Benzil	$C_2H_5O_2H$, NaOH	Benzoic acid, ethyl benzoate	94 70	158
		CH_3CO_3H	Benzoic acid	95	61, 70
		H_2O_2, CH_3CO_2H, $HClO_4$	Benzoic acid	83	6
$C_{15}H_{12}O_2$	1,3-Diphenylpropane-1,2-dione	$C_2H_5O_2H$, NaOH	Benzoic acid, phenylacetic acid	61	158
$C_{15}H_{12}O_3$	p-Methoxybenzil	$C_2H_5O_2H$, NaOH	Anisic acid, benzoic acid	79	158
$C_{16}H_{14}O_4$	Anisil	$C_2H_5O_2H$, NaOH	Anisic acid, ethyl anisoate	70	158
		H_2O_2, CH_3CO_2H	Anisic acid	66	6
$C_{18}H_{14}O_2$	Dicinnamylidenebiacetyl	Perphthalic acid	2-Styrylacrylic anhydride	26	66

Note: References 138-164 are listed on p. 106.

TABLE V—Continued

BAEYER-VILLIGER OXIDATION OF POLYCARBONYL COMPOUNDS

Carbonyl Compound		Reagent	Product	Yield, %	Reference
α-Diketones—Continued					
$C_{18}H_{18}O_2$	1-Mesityl-3-phenylpropane-1,2-dione	$C_2H_5O_2H$, NaOH	Phenylacetic acid, β-isodurylic acid	70	153
$C_{18}H_{32}O_4$	9,10-Diketostearic acid	CH_3CO_2H	Pelargonic acid, azelaic acid	90–95	61
$C_{21}H_{32}O_5$	3β,14-Dihydroxy-14-iso-20-keto-17-iso-pregnan-21-carboxylic acid	H_2O_2, CH_3CO_2H	3β,14-Dihydroxy-14-iso-17-isoetiocholanic acid	27	63
$C_{23}H_{32}O_6$	3β-Acetoxy-14-hydroxy-14-iso-20-keto-pregnan-21-carboxylic acid lactone	H_2O_2, $KHCO_3$	3β,14-Dihydroxy-14-iso-17-isoetiocholanic acid	90	63
		H_2O_2, CH_3CO_2H	3β-Acetoxy-14-hydroxy-14-iso-17-isoetiocholanic acid	—	63
β-Diketones					
$C_5H_8O_2$	Acetylacetone	CH_3CO_2H	Ethanol	—	77
$C_6H_{10}O_3$	Ethyl acetoacetate	CH_3CO_2H	Ethyl hydrogen oxalate, ethanol	—	77
$C_7H_{12}O_2$	3,3-Dimethylpentane-2,4-dione	CH_3CO_2H	No reaction	—	77
$C_7H_{12}O_3$	Ethyl α-methylacetoacetate	CH_3CO_2H	Ethyl hydrogen oxalate	—	77
$C_8H_{14}O_3$	Ethyl α,α-dimethylacetoacetate	CH_3CO_2H	No reaction	—	77
$C_9H_{14}O_5$	Ethyl acetonedicarboxylate	H_2O_2, $(C_2H_5)_2O$	Oxalic acid	—	73
$C_{11}H_8O_3$	2-Acetylindan-1,3-dione	CH_3CO_3H	2-Acetoxyindan-1,3-dione	64	77
$C_{11}H_{12}O_3$	Ethyl benzoylacetate	CH_3CO_3H	Benzoic acid, ethyl oxalate	—	77
$C_{13}H_{16}O_3$	Ethyl α-benzoylacetoacetate	CH_3CO_3H	Ethyl hydrogen oxalate, methylbenzylcarbinol	—	77
$C_{14}H_{20}O_2$	(spirocyclohexanone–cyclopentane structure)	H_2O_2, CH_3CO_2H	CH_2-CH_2 / CO_2H HO_2C (cyclopentane dicarboxylic structure)	87	118
$C_{15}H_{22}O_4$	1-Isovaleryl-2,4,6-triketo-3,3,5,5-tetramethyl-cyclohexane (leptospermone)	H_2O_2, pyridine	2,4,6-Triketo-3,3,5,5-tetramethylcyclohexyl isovalerate	12	70
$C_{16}H_{10}O_3$	2-Benzoylindan-1,3-dione	H_2O_2, $(C_2H_5)_2O$	2-Benzoyloxyindan-1,3-dione	66	78
$C_{17}H_{14}O_3$	Acetyldibenzoylmethane	H_2O_2, $(C_2H_5)_2O$	No reaction	—	78
$C_{23}H_{16}O_3$	Tribenzoylmethane	H_2O_2, NaOH	Benzoic acid	62	78

Note: References 138–164 are listed on p. 100.

TABLE VI

BAEYER-VILLIGER OXIDATION OF ALDEHYDES

	Carbonyl Compound	Reagent	Product	Yield, %	Reference
CH_2O	Formaldehyde	CH_3CO_3H	Formic acid	Quantitative	80
C_2H_4O	Acetaldehyde	H_2O_2, NaOH	Formic acid, hydrogen	—	89, 87
		$C_2H_5CO_3H$	Acetic acid	—	81
		H_2O_2, H_2SO_4	Acetic acid, formic acid, methane, hydrogen, carbon dioxide	—	88
$C_2H_4O_2$	Glycolic aldehyde	H_2O_2	Hydrogen, carbon dioxide, formic acid, unidentified acids	—	86
C_3H_6O	Propionaldehyde	H_2O_2, H_2SO_4	Propionic acid, acetic acid, formic acid, hydrogen, carbon dioxide, ethane	—	88
$C_5H_{10}O$	Pivalic aldehyde	H_2O_2	Isobutane, hydrogen, carbon monoxide, unidentified acids	—	86
$C_7H_4Br_2O_2$	3,5-Dibromo-2-hydroxybenzaldehyde	H_2O_2, NaOH	3,5-Dibromocatechol	—	52
	3,5-Dibromo-4-hydroxybenzaldehyde	H_2O_2, NaOH	3,5-Dibromohydroquinone	—	52
	4,6-Dibromo-2-hydroxybenzaldehyde	H_2O_2, NaOH	4,6-Dibromocatechol	—	52
$C_7H_4Cl_2O_2$	3,5-Dichloro-4-hydroxybenzaldehyde	H_2O_2, NaOH	3,5-Dichlorohydroquinone	—	52
	3,5-Dichloro-2-hydroxybenzaldehyde	H_2O_2, NaOH	3,5-Dichlorocatechol	—	159, 52
$C_7H_4I_2O_2$	3,5-Diiodo-4-hydroxybenzaldehyde	H_2O_2, NaOH	No reaction	—	52
$C_7H_5BrO_2$	5-Bromo-2-hydroxybenzaldehyde	H_2O_2, NaOH	5-Bromocatechol	—	52
	3-Bromo-4-hydroxybenzaldehyde	H_2O_2, NaOH	Bromohydroquinone	60–70	52
$C_7H_5ClO_3$	5-Chloro-2-hydroxybenzaldehyde	H_2O_2, NaOH	5-Chlorocatechol	—	52
$C_7H_5NO_3$	o-Nitrobenzaldehyde	CH_3CO_3H	o-Nitrobenzoic acid	99	91
	m-Nitrobenzaldehyde	CH_3CO_3H	m-Nitrobenzoic acid	90	91
$C_7H_5NO_4$	3-Nitro-2-hydroxybenzaldehyde	H_2O_2, NaOH	3-Nitrocatechol	—	52
	5-Nitro-2-hydroxybenzaldehyde	H_2O_2, NaOH	5-Nitrocatechol	70	52
	2-Nitro-3-hydroxybenzaldehyde	H_2O_2, NaOH	No reaction	—	52
	2-Nitro-4-hydroxybenzaldehyde	H_2O_2, NaOH	Nitrobenzoquinone	—	52
	3-Nitro-4-hydroxybenzaldehyde	H_2O_2, NaOH	No reaction	—	52
C_7H_6O	Benzaldehyde	H_2SO_5	Benzaldehyde peroxide	—	52
		H_2O_2, $(C_2H_5)_2O$	Benzoic acid, phenol	40	160, 140
		CH_3CO_3H	Benzoic acid	Quantitative	92, 161
$C_7H_6O_2$	Salicylaldehyde	H_2O_2, CH_3COCH_3	Salicylic acid, catechol	70, trace	80, 86

Note: References 108–161 are listed on p. 106.

TABLE VI—Continued

BAEYER-VILLIGER OXIDATION OF ALDEHYDES

	Carbonyl Compound	Reagent	Product	Yield, %	Reference
$C_7H_6O_2$	Salicylaldehyde (Contd.)	H_2O_2, pyridine	Salicylic acid, catechol	75, 20	95
		H_2O_2, NaOH	Catechol	Quantitative	52, 131
		CH_3CO_3H	Catechol	89	102, 91, 95
	m-Hydroxybenzaldehyde	H_2O_2, NaOH	No reaction		52
		CH_3CO_3H	m-Hydroxybenzoic acid	74	91
	p-Hydroxybenzaldehyde	H_2O_2, NaOH	Hydroquinone	Quantitative	52
		CH_3CO_3H	Hydroquinone	93	80, 91
		H_2O_2, NaOH	Hydroquinone		52
$C_7H_6O_3$	2,4-Dihydroxybenzaldehyde	H_2O_2, NaOH	Hydroxyhydroquinone		52
	3,4-Dihydroxybenzaldehyde	H_2O_2, NaOH	Hydroxyhydroquinone	31	93
C_7H_7NO	o-Aminobenzaldehyde	H_2SO_3	o-Aminophenyl formate, o-aminophenol, anthranil	88	90
$C_7H_{14}O$	n-Heptanal	CH_3CO_3H	n-Heptanoic acid		11
		H_2O_2, $(C_2H_5)_2O$	α-Hydroxyheptylhydroperoxide	60	129
$C_8H_6O_3$	Piperonal	CH_3CO_3H	3,4-Methylenedioxyphenol	70	91
	2-Hydroxy-4-methylbenzaldehyde	CH_3CO_3H	4-Methylcatechol	51	91
	2-Hydroxy-5-methylbenzaldehyde	CH_3CO_3H	5-Methylcatechol	45	52
$C_8H_6BrO_3$	3-Bromo-4-hydroxy-5-methoxybenzaldehyde	H_2O_2, NaOH	3-Bromo-5-methoxyhydroquinone		52
$C_8H_5NO_5$	2-Nitro-4-hydroxy-3-methoxybenzaldehyde	H_2O_2, NaOH	3-Methoxy-2-nitrohydroquinone		52
	3-Nitro-4-hydroxy-5-methoxybenzaldehyde	H_2O_2, NaOH	No reaction		163
C_8H_8O	Phenylacetaldehyde	H_2O_2	Benzyl alcohol, formic acid		163
		H_2O_2, heat	Phenylacetic acid, benzaldehyde, formic acid, benzole acid		163
$C_8H_8O_2$	o-Methoxybenzaldehyde	H_2O_2, $(C_2H_5)_2O$	Guaiacol, o-methoxybenzoic acid		92
		CH_3CO_3H	Guaiacol formate	99	91
	p-Methoxybenzaldehyde	H_2O_2, $(C_2H_5)_2O$	Hydroquinone monomethyl ether, p-methoxybenzole acid		92
		CH_3CO_3H	p-Methoxybenzoic acid	Quantitative	80
$C_8H_8O_3$	2-Hydroxy-3-methoxybenzaldehyde	H_2O_2, NaOH	3-Methoxycatechol	69–80	135
	2-Hydroxy-5-methoxybenzaldehyde	H_2O_2, NaOH	4-Methoxycatechol		159
	3-Hydroxy-4-methoxybenzaldehyde	H_2O_2, NaOH	4-Methoxyresorcinol (?)		52
	Vanillin	H_2O_2, NaOH	Methoxyhydroquinone	Quantitative	52

TABLE VI—*Continued*

BAEYER-VILLIGER OXIDATION OF ALDEHYDES

Carbonyl Compound	Reagent	Product	Yield, %	Reference
$C_9H_{10}O_3$				
2,4-Dimethoxybenzaldehyde	$H_2O_2, (C_2H_5)_2O$	2,4-Dimethoxyphenol	27	92
3,4-Dimethoxybenzaldehyde	$H_2O_2, (C_2H_5)_2O$	3,4-Dimethoxyphenol, 3,4-dimethoxybenzoic acid	—	92
	CH_3CO_3H	3,4-Dimethoxyphenol	66	90, 91
$C_9H_{18}O$				
Pelargonic aldehyde	$H_2O_2, (C_2H_5)_2O$	α-Hydroxynonylhydroperoxide	—	11
$C_{10}H_{12}O_3$				
3-Ethoxy-4-methoxybenzaldehyde	CH_3CO_3H	3-Ethoxy-4-methoxyphenol	—	90
$C_{10}H_{12}O_4$				
2,4,5-Trimethoxybenzaldehyde	$H_2O_2, (C_2H_5)_2O$	2,4,5-Trimethoxyphenol	18	92
$C_{10}H_{20}O$				
Capric aldehyde	$H_2O_2, (C_2H_5)_2O$	α-Hydroxydecylhydroperoxide	—	11
$C_{11}H_{14}O_3$				
3,4-Dimethoxy-6-ethylbenzaldehyde	$H_2O_2, (C_2H_5)_2O$	3,4-Dimethoxy-6-ethylphenol, 3,4-dimethoxy-6-ethylbenzoic acid	—	92
$C_{11}H_{22}O$				
Undecylic aldehyde	$H_2O_2, (C_2H_5)_2O$	α-Hydroxyundecylhydroperoxide	—	11
$C_{12}H_{16}O_3$				
4-Butoxy-3-methoxybenzaldehyde	CH_3CO_3H	4-Butoxy-3-methoxyphenol	68	90
$C_{12}H_{24}O$				
Lauric aldehyde	$H_2O_2, (C_2H_5)_2O$	α-Hydroxydodecylhydroperoxide	—	11
$C_{14}H_{11}NO_5S$				
4-Nitro-2(p-tolylthio)benzaldehyde	H_2O_2, CH_3CO_2H	4-Nitro-2(p-toluenesulphonyl) benzoic acid	—	164
$C_{15}H_{10}O_2$				
3-Hydroxy-4-formylphenanthrene	$H_2O_2, NaOH$	3,4-Dihydroxyphenanthrene	80	94

Note: References 138-164 are listed on p. 106.

REFERENCES TO TABLES

[138] Baeyer and Villiger, *Ber.*, **33**, 858 (1900).

[139] Baeyer and Villiger, *Ber.*, **33**, 124 (1900).

[140] Dilthey, Inckel, and Stephan, *J. prakt. Chem.*, [2] **154**, 219 (1940).

[141] Friess, *J. Am. Chem. Soc.*, **71**, 14 (1949).

[142] Marker, *J. Am. Chem. Soc.*, **62**, 2621 (1940).

[143] Buchi and Jeger, *Helv. Chim. Acta*, **32**, 540 (1949).

[144] Karrer and Haab, *Helv. Chim. Acta*, **32**, 973 (1949).

[145] Schroeter, German pat. 562,827 (*Chem. Zentr.*, I, 1933, 127).

[146] Stoll and Scherrer, *Helv. Chim. Acta*, **13**, 142 (1930).

[147] Jacobsen, Picha, and Levy, *J. Biol. Chem.*, **171**, 81 (1947).

[148] Burckhardt and Reichstein, *Helv. Chim. Acta*, **25**, 821 (1942).

[149] Windaus, *Ber.*, **37**, 2027 (1904).

[150] Dakin, *Proc. Chem. Soc.*, **25**, 194 (1909).

[151] Hassall and Todd, *J. Chem. Soc.*, 1947, 611.

[152] Inagaki, *J. Pharm. Soc. Japan*, **59**, 7 (1939) [*C. A.*, **33**, 3790 (1939)].

[153] Böeseken and Kremer, *Rec. trav. chim.*, **50**, 827 (1931).

[154] Karrer and Hohl, *Helv. Chim. Acta*, **32**, 1028 (1949).

[155] Karrer and Testa, *Helv. Chim. Acta*, **32**, 1019 (1949).

[156] Charrier and Beretta, *Gazz. chim. ital.*, **54**, 988 (1924).

[157] Dimroth and Goldschmidt, *Ann.*, **399**, 62 (1913).

[158] Barnes and Lewis, *J. Am. Chem. Soc.*, **58**, 947 (1936).

[159] Kvalnes, *J. Am. Chem. Soc.*, **56**, 2487 (1934).

[160] Baeyer and Villiger, *Ber.*, **33**, 2484 (1900).

[161] Sandonnini and Giacomello, *Atti reale accad. naz. Lincei*, [6] **19**, 43 (1934) (*Chem. Zentr.*, II, 1934, 234).

[162] Wacek, Eppinger, and Bezard, *Ber.*, **73**, 521 (1940).

[163] Cattaneo, *Gazz. chim. ital.*, **64**, 509 (1934).

[164] Campbell, Dick, Ferguson, and Louden, *J. Chem. Soc.*, 1941, 747.

CHAPTER 4

THE ALKYLATION OF ESTERS AND NITRILES

Arthur C. Cope, H. L. Holmes, and Herbert O. House

Massachusetts Institute of Technology

CONTENTS

INTRODUCTION†

This chapter is concerned with the reactions of metal salts (enolates) of active methylene compounds with alkylating agents such as alkyl halides to produce alkyl derivatives. The first example of this reaction is found in the literature of 1863 when Geuther prepared ethyl α-ethyl

---

* To avoid confusion in the naming of disubstituted active methylene compounds containing two unlike substituents, the name of one of the substituents has been parenthesized.

† The authors are indebted to Morton Brown, Norman A. Le Bel, and Theodor A. Liss for checking the literature referred to in the final draft of this chapter.

This ionic resonance hybrid is often called the enolate anion. It may be formed by reaction of the base with either the keto or the enol form of the active methylene compound.[4]

The acidity of active methylene compounds can be attributed to resonance stabilization of the enolate anion, a stabilizing interaction not possible with the un-ionized form. The degree to which various substituent groups enhance the acidity of active methylene compounds appears to decrease in the following order: $-NO_2 > -\underset{\underset{O}{\|}}{C}-R > -C\equiv N > -CO_2C_2H_5 >$

$-C_6H_5$. The substitution of two or three such groups on a carbon atom further augments the acidity of the remaining hydrogen atoms bound to the same carbon atom. This effect would be anticipated if the additional resonance stabilization available to such a polysubstituted enolate anion is considered (see, however, p. 133). On the other hand, substitution of aliphatic groups at the active methylene carbon atom reduces the acidity of the remaining hydrogen atom. The effect of a number of substituents (R) on the acid strength of monosubstituted acetic esters ($RCH_2CO_2C_2H_5$) has been measured;[5] the compounds decreased in acidity in the following order: $R = C_6H_5 > H > CH_3 > C_2H_5 > n\text{-}C_3H_7 > n\text{-}C_{10}H_{21} > n\text{-}C_{16}H_{33} > \text{cyclohexyl} > i\text{-}C_3H_7$. It is noteworthy that branching of the carbon chain ($R = i\text{-}C_3H_7$) has a greater effect on acidity than the length of the carbon chain ($R = n\text{-}C_{16}H_{33}$). A similar reduction in the acidity of substituted acetic acids has been ascribed to steric hindrance to solvation of the carboxylate anion.[6] This explanation would appear to be equally valid for the increased difficulty with which highly substituted acetic esters are converted to their enolate anions.

The formation of the enolate anion, the reactive derivative of the active methylene compound in alkylation reactions, results from an equilibrium reaction between the base and the active methylene compound. Competing equilibra involve the solvent (i.e., ROH, NH_3, etc.) and either the base or the enolate anion. As a consequence of these equilibria, both the

$$B^{\ominus} + CH_2(CO_2C_2H_5)_2 \rightleftharpoons BH + \overset{\ominus}{C}H(CO_2C_2H_5)_2$$
$$\overset{\ominus}{C}H(CO_2C_2H_5)_2 + ROH \rightleftharpoons CH_2(CO_2C_2H_5)_2 + \overset{\ominus}{O}R$$

$$B^{\ominus} + ROH \rightleftharpoons BH + \overset{\ominus}{O}R$$
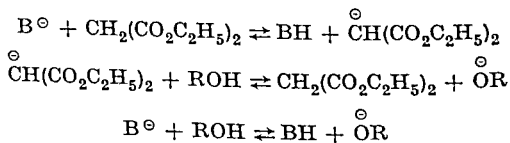
solvent (i.e., ROH) and the conjugate acid (BH) of the base must be much

[4] Alexander, *Principles of Ionic Organic Reactions*, John Wiley & Sons, New York, 1950, pp. 132–134.

[5] Brown and Eberly, *J. Am. Chem. Soc.*, **62**, 113 (1940).

[6] Hammond and Hogle, *J. Am. Chem. Soc.*, **77**, 338 (1955).

weaker acids than the active methylene compound if an adequate concentration of the enolate anion is to be present in the reaction mixture.

All available evidence indicates that the enolate anion of the active methylene compound reacts with the alkylating agent by a bimolecular nucleophilic displacement (S_N2) process.[7-9] Therefore the structure of the alkylating agent may be expected to influence the course of the alkylation reaction in a manner analogous to the effect of structure on other

$$(C_2H_5O_2C)_2CH^{\ominus} + \underset{\substack{H\\H}}{\overset{CH_3}{C}}{-Br} \rightarrow$$

$$(C_2H_5O_2C)_2CH-\overset{CH_3}{\underset{H}{C}}{--H} + Br^{\ominus}$$
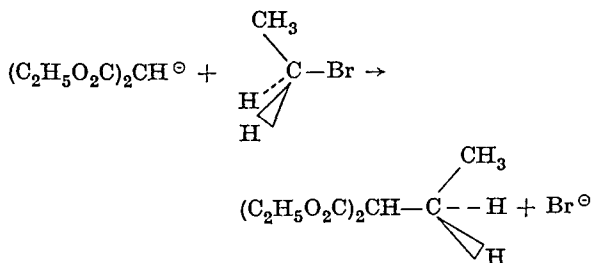
S_N2 reactions. Thus, inversion of configuration is noted when the displacement occurs at an asymmetric center. Diethyl 3α-cholestanylmalonate was produced by the reaction of 3β-cholestanyl tosylate with

$$p\text{-}CH_3C_6H_4SO_3 \quad \cdots + \overset{\ominus}{CH}(CO_2C_2H_5)_2 \longrightarrow$$

$$(C_2H_5O_2C)_2CH \quad \cdots + p\text{-}CH_3C_6H_4SO_3^{\ominus}$$

$$+ \overset{\ominus}{CH}(CO_2C_2H_5)_2 \longrightarrow$$

$$\xrightarrow{H^{\oplus}}$$

[7] Grigsby, Hind, Chanley, and Westheimer, *J. Am. Chem. Soc.*, **64**, 2606 (1942).
[8] Newman and VanderWerf, *J. Am. Chem. Soc.*, **67**, 233 (1945).
[9] Bartlett in Gilman, *Organic Chemistry*, Vol. 3, John Wiley & Sons, New York, 1953, p. 25.

diethyl sodiomalonate.[10]   Similarly, the reaction of cyclopentene oxide yielded diethyl *trans*-(2-hydroxycyclopentyl)malonate.[7]   The attack of the enolate anion occurs at the less hindered of the two possible positions in ethylene oxides; displacement occurred at the primary carbon atom with both styrene oxide and *p*-nitrostyrene oxide.[11,12]   The hindrance to

$$R\langle\rangle CH\!-\!CH_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow$$

(R = H or NO$_2$)

$$R\langle\rangle CHCH_2CHCO_2C_2H_5$$
$$\quad\quad\quad\quad\quad |\quad\quad\quad\quad| $$
$$\quad\quad\quad\quad\quad O\!-\!-\!-CO$$

rearward attack presented by tertiary alkyl halides usually limits the usefulness of the alkylation reaction to primary and secondary alkylating agents (p. 124).   When treated with a solution of diethyl sodiomalonate in ethanol, *n*-butyl bromide, *sec*-butyl bromide, and *t*-butyl bromide formed the corresponding diethyl butylmalonates in yields of 80–90%,[13] 80–81%,[14] and 6.4%,[15] respectively.

Only in special instances has the course of the reaction deviated from the path expected on the basis of a normal bimolecular nucleophilic displacement.   The reaction of certain allyl halides with enolate anions has been observed to yield mixtures of products.   Although 1-chloro-2-pentene reacted with the diethyl malonate anion to yield only the expected product, the isomeric 3-chloro-1-pentene formed both the product of direct displacement and the product resulting from attack of the enolate at the 1-position in an S_N2' displacement.[16,17]

$$C_2H_5CH\!=\!CHCH_2Cl + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow C_2H_5CH\!=\!CHCH_2CH(CO_2C_2H_5)_2$$

$$\overset{\displaystyle Cl}{\underset{\displaystyle |}{}} $$

$$C_2H_5\!-\!\underset{\displaystyle |S_N2\;\;\;|S_N2'}{CH}\!-\!CH\!=\!CH_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \xrightarrow{S_N2\ process} C_2H_5\!-\!CH\!-\!CH\!=\!CH_2$$
$$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad |$$
$$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad CH(CO_2C_2H_5)_2$$

S_N2' process

[16] Shoppee and Stephenson, *J. Chem. Soc.*, **1954**, 2231.

[11] Van Zyl and van Tamelen, *J. Am. Chem. Soc.*, **72**, 1357 (1950).

[12] Cristol and Helmreich, *J. Am. Chem. Soc.*, **74**, 4083 (1952).

[13] Adams and Kamm, *Org. Syntheses, Coll. Vol.* 1, John Wiley & Sons, New York, 1941, p. 250.

[14] Vliet, Marvel, and Hsueh, *Org. Syntheses, Coll. Vol.* 2, John Wiley & Sons, New York, 1943, p. 417.

[15] Dox and Bywater, *J. Am. Chem. Soc.*, **58**, 731 (1936).

[16] Winstein, *Bull. soc. chim. France*, **1951**, C43.

[17] Kepner, Winstein, and Young, *J. Am. Chem. Soc.*, **71**, 115 (1949).

When, in similar systems, the halogen was bonded to a tertiary carbon atom, as in linalyl chloride[18] or linalyl bromide,[19] only the product resulting from an S_N2' displacement was observed.

$$(CH_3)_2C\!\!=\!\!CHCH_2CH_2CBr(CH_3)CH\!\!=\!\!CH_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow$$

$$(CH_3)_2C\!\!=\!\!CHCH_2CH_2C(CH_3)\!\!=\!\!CHCH_2CH(CO_2C_2H_5)_2$$
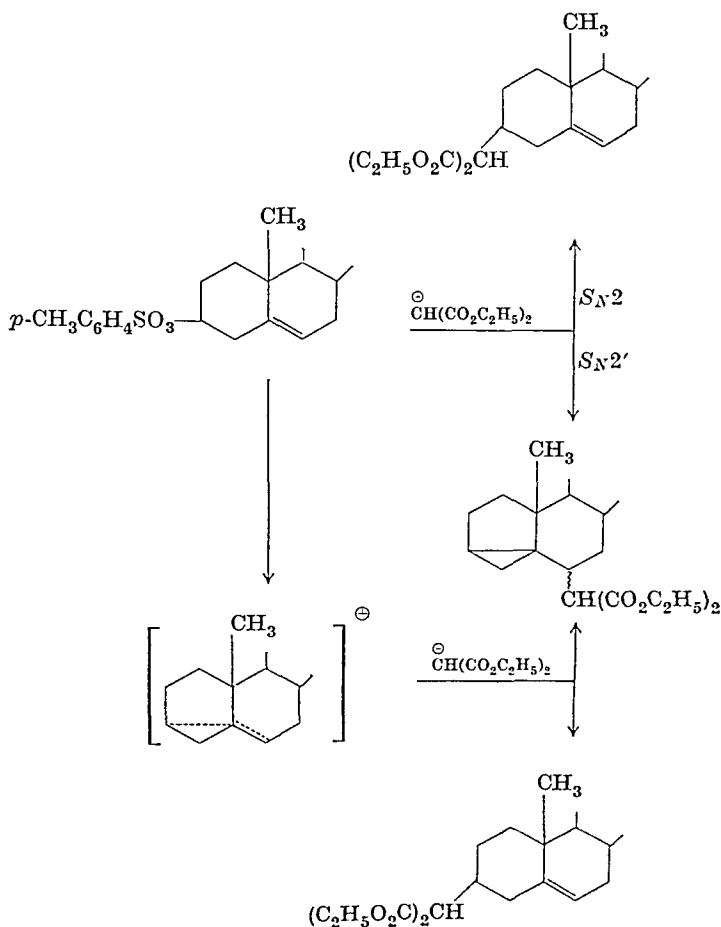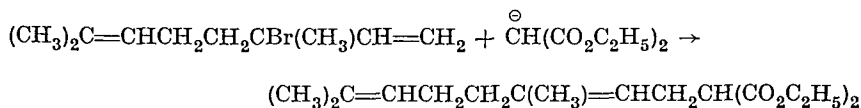
[18] Barnard and Bateman, *J. Chem. Soc.*, **1950**, 926.
[19] Dupont and Labaune, *Chem. Zentr.*, **82**, II, 138 (1911).

A displacement of the S_N2' type has been postulated to explain the products formed when 1,4-dibromo-2-butene reacted with diethyl sodiomalonate (p. 141).[20] A more complicated example of an abnormal alkylation is provided by the reaction of 3β-cholesteryl tosylate with diethyl sodiomalonate. The products initially reported,[21,22] diethyl 3-cholesterylmalonate (later shown to be the α-isomer[10]) and diethyl 3,5-cyclo-6-cholestanylmalonate, seemed best explained by the simultaneous operation of S_N2 and S_N2' displacements.[23] However, the demonstration[10] that the diethyl 3-cholesterylmalonate fraction is composed mainly of the 3β-isomer suggests the intervention of an intermediate cholesteryl ion (shown in brackets in the equation on page 113) prior to attack by the enolate anion. A similar anomaly was observed when β-haloamines were used as alkylating agents. When diphenylacetonitrile was alkylated either with 1-dimethylamino-2-chloropropane or with 2-dimethylamino-1-chloropropane similar mixtures of products were obtained.[24-26] Such a result suggests the formation of a cyclic immonium ion[27] prior to the alkylation step.

$$(CH_3)_2NCH_2CH(CH_3)Cl \rightarrow \left[\begin{array}{c} CH_2\!-\!CHCH_3 \\ \diagdown N \diagup \\ CH_3 \quad CH_3 \end{array} \right]^{\oplus} Cl^{\ominus}$$

$$(CH_3)_2NCH(CH_3)CH_2Cl \rightarrow$$

$$(C_6H_5)_2CHCN \bigg| \begin{array}{c} NaNH_2 \\ C_6H_6 \end{array}$$

$$(C_6H_5)_2C(CN)CH(CH_3)CH_2N(CH_3)_2 + (C_6H_5)_2C(CN)CH_2CH(CH_3)N(CH_3)_2$$
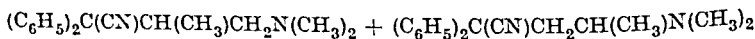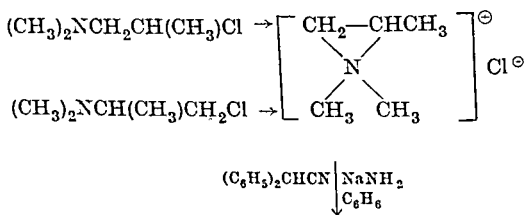
The alkylation of alkylidene derivatives may be considered a variant of the reaction of monoalkylated sodiomalonic esters with alkylating agents. With the alkylidene derivatives the alkyl group is invariably introduced at the position *alpha* to the activating group with attendant migration of the double bond to the β,γ-position.[28]

[20] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, 1952, 3610.
[21] Kaiser and Svarz, *J. Am. Chem. Soc.*, 67, 1309 (1945).
[22] Svarz and Kaiser, *J. Am. Chem. Soc.*, 69, 847 (1947).
[23] Corey and Sneen, *J. Am. Chem. Soc.*, 75, 6234 (1953).
[24] Schultz and Sprague, *J. Am. Chem. Soc.*, 70, 48 (1948).
[25] Attenburrow, Elks, Hems, and Speyer, *J. Chem. Soc.*, 1949, 510.
[26] Walton, Ofner, and Thorp, *J. Chem. Soc.*, 1949, 648.
[27] Schultz, Robb, and Sprague, *J. Am. Chem. Soc.*, 69, 2454 (1947).
[28] Cope, Hartung, Hancock, and Crossley, *J. Am. Chem. Soc.*, 62, 314 (1940).

$$CH_3CH_2CH=C(CO_2C_2H_5)_2 + \overset{\ominus}{O}C_2H_5 \rightleftharpoons C_2H_5OH +$$

$$\overset{\ominus}{C}H_3CHCH=C\overset{\displaystyle \overset{O}{\|}}{\underset{\displaystyle \underset{O}{\|}}{\overset{COC_2H_5}{COC_2H_5}}} \leftrightarrow CH_3CH=CH-\overset{\ominus}{C}\overset{\displaystyle \overset{O}{\|}}{\underset{\displaystyle \underset{O}{\|}}{\overset{COC_2H_5}{COC_2H_5}}}$$

$$\leftrightarrow CH_3CH=CH-C\overset{\displaystyle \overset{\overset{\ominus}{O}}{|}}{\underset{\displaystyle \underset{O}{\|}}{\overset{COC_2H_5}{COC_2H_5}}}$$

$$\Big\downarrow n\text{-}C_3H_7I$$

$$CH_3CH=CH-\underset{\displaystyle \underset{C_3H_7\text{-}n}{|}}{C}(CO_2C_2H_5)_2$$
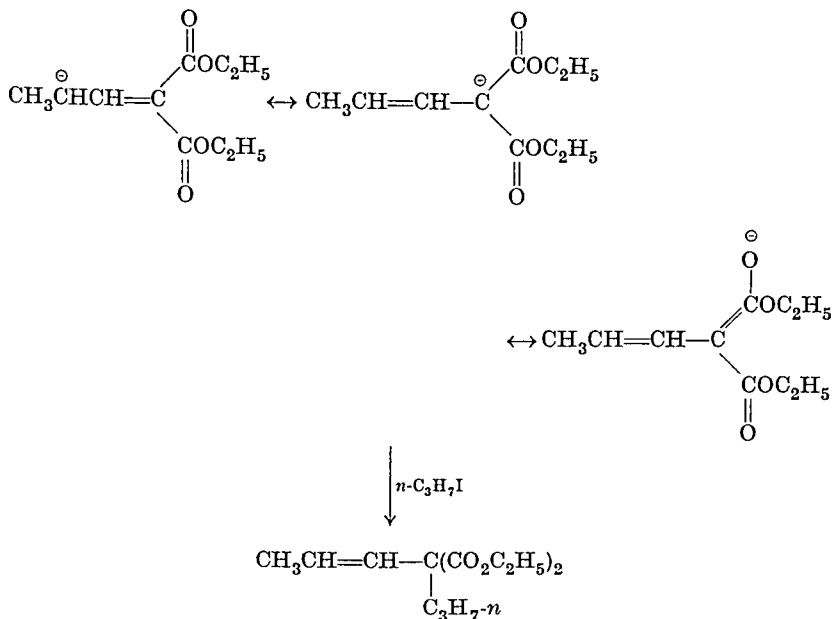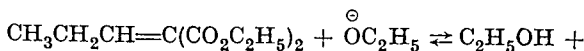
SCOPE AND LIMITATIONS

General Considerations

Nature of the Base and Solvent. If an alkylation reaction proceeds by the bimolecular mechanism described earlier (p. 111), the rate of alkylation will be directly proportional to the molar concentration of the enolate ion present in the reaction mixture. When the enolate concentration is small, various side reactions, to be described later (p. 123), will predominate. Since the concentration of the enolate ion is dependent upon equilibria involving the base, the solvent, and the active methylene compound (p. 110), the correct choice of base and solvent is of prime importance if the alkylation reaction is to be successful. Usually the base and solvent chosen are such that both the conjugate acid of the base and the solvent are weaker acids than the active methylene compound. Such a choice assures a high concentration of the enolate anion.

In several instances the rate of alkylation of β-keto esters has been found to depend on the nature of the cationic portion of the base employed.[29] This effect has been ascribed to the formation of a chelate structure, composed of the cation and the enolate anion, which subsequently reacts

with the alkyl halide.[29]   Alternatively, the effect of the cation on the rate of alkylation might be attributed to the association of the cation and the enolate anion as ion pairs in the non-polar solvents where the effect of the cation is most pronounced.[30]   If such ion pairs are less effective than the free enolate anions as nucleophilic reagents, then the rate of alkylation would depend on the extent to which the cation and enolate anion are associated as ion pairs, a property which would be a function of the particular cation employed in a given solvent system.

The reagents most commonly used to prepare the enolates of active methylene compounds include the metal alkoxides and the more basic metal amides, sodium triphenylmethide and sodium hydride, as well as metallic sodium and metallic potassium.   A meaningful comparison of relative base strengths can best be made in terms of various base-solvent systems, since the basicity is influenced by the solvent.   Many of the comparisons of relative basicity made in this chapter are founded on the success or failure of various bases in certain alkylation reactions, because data concerning relative basicities are not available.   Consideration of the enolate-base-solvent equilibria mentioned earlier (p. 110) will make apparent the possibility of increasing the concentration of the enolate anion in the reaction mixture if the solvent is replaced by a solvent of lower acidity.   This possibility has been exploited in several instances[31-33] where alkylation was either unsuccessful or difficult with alcohol as the solvent; replacement of the alcohol with a less acidic solvent such as ether or benzene permitted alkylation to occur.   If possible, the base and the enolate should be soluble in the solvent chosen.   Otherwise, the surface of the basic reagent may become coated with the metal enolate, preventing further reaction.

The metal alkoxides are usually sufficiently strong bases for use in the alkylation of malonic esters, cyanoacetic esters, malononitriles, and certain mononitriles.   The commonly employed metal alkoxides appear to increase in basicity in the following order:[34-37] $CH_3ONa < CH_3CH_2ONa < (CH_3)_2CHONa < (CH_3)_3COK$.   When the active methylene compound and/or the alkylating agent contain one or more ester functions, the alkoxide chosen should correspond to the alkoxyl group of the ester.

[29] Brändstrom, Acta Chem. Scand., 7, 223 (1953).
[30] James Cason, private communication.
[31] Wagner-Jauregg and Arnold, Ann., 529, 274 (1937).
[32] Adams, Stanley, and Stearns, J. Am. Chem. Soc., 50, 1475 (1928).
[33] Pearson, J. Am. Chem. Soc., 71, 2212 (1949).
[34] Janssen, Ann., 250, 125 (1888).
[35] Kopp and Tchoubar, Bull. soc. chim. France, 1951, 30.
[36] McEwen, J. Am. Chem. Soc., 58, 1124 (1936).
[37] Cope and Hancock, J. Am. Chem. Soc., 60, 2903 (1938).

Otherwise a nonhomogeneous product will result from the ester inter-change which takes place concurrently with alkylation.[37-41] This problem

$$CH_2(CN)CO_2C_2H_5 + i\text{-}C_5H_{11}O^{\ominus} \rightleftharpoons CH_2(CN)C\underset{\overset{\diagup OC_2H_5}{\diagdown OC_5H_{11}\text{-}i}}{-}O^{\ominus}$$

$$\updownarrow$$

$$C_2H_5O^{\ominus} + CH_2(CN)CO_2C_5H_{11}\text{-}i$$
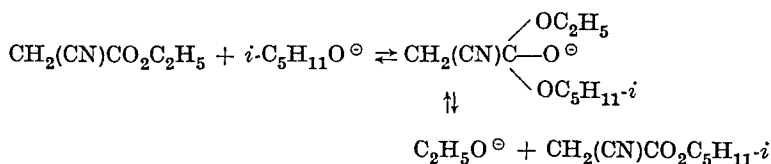
is least serious when the highly branched t-butoxide anion is employed. Several cases have been reported in which the use of sodium t-butoxide in t-butyl alcohol led to the successful alkylation of ethyl esters that could not be alkylated readily with sodium ethoxide in ethanol.[35]

The sodium and potassium alkoxides are normally prepared and used in an excess of the corresponding anhydrous[13,42] alcohol which serves as the solvent. However, the advantages to be gained from the use of other solvents should not be overlooked. The decarbethoxylation of malonic and cyanoacetic esters in the presence of ethoxide ion, to be discussed more fully later (p. 127), which sometimes occurs as a side reaction, can be diminished if diethyl carbonate is used as the reaction solvent.[43,44] In addition, the high boiling point of diethyl carbonate permits the reaction time to be shortened. In general, the low yields obtained from slow alkylation reactions (e.g., with long-chain alkyl halides as the alkylating agents) are improved if the low-boiling solvent, ethanol or ether, is replaced by a higher-boiling solvent such as n-butyl alcohol[45,46] or diethyl carbonate,[43,44,47-51] or if the reaction mixture is heated in a sealed tube.[31,52] However, higher reaction temperatures sometimes favor dialkylation[53] and dehydrohalogenation of the alkylating agent.[54]

[38] Hessler, *J. Am. Chem. Soc.*, **38**, 909 (1916).

[39] Hessler and Lamb, *J. Am. Chem. Soc.*, **43**, 205 (1921).

[40] Hessler and Henderson, *J. Am. Chem. Soc.*, **43**, 672 (1921).

[41] Osman and Cope, *J. Am. Chem. Soc.*, **66**, 881 (1944).

[42] Gyngell, Phillips, and Smith, *Ind. Chemist*, **21**, 526 (1945).

[43] Wallingford, Homeyer, and Jones, *J. Am. Chem. Soc.*, **63**, 2056 (1941).

[44] Wallingford, Thorpe, and Homeyer, *J. Am. Chem. Soc.*, **64**, 580 (1942).

[45] Bleyberg and Ulrich, *Ber.*, **64**, 2504 (1931).

[46] Backer and Strating, *Rec. trav. chim.*, **59**, 933 (1940).

[47] Simon, Kaufmann, and Schinz, *Helv. Chim. Acta*, **29**, 1133 (1946).

[48] Plattner, Fürst, Wyss, and Sandrin, *Helv. Chim. Acta*, **30**, 689 (1947).

[49] Wiss and Fuchs, *Helv. Chim. Acta*, **35**, 407 (1952).

[50] Blicke and Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946).

[51] Wallingford and Homeyer, U.S. pat. 2,358,768 [*C. A.*, **39**, 1879 (1945)].

[52] Marshall, *J. Chem. Soc.*, **1931**, 2336.

[53] Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

[54] Cope and McElvain, *J. Am. Chem. Soc.*, **54**, 4311 (1932).

The increase in the enolate concentration which results when an alcohol is replaced by a much less acidic or an inert solvent has already been mentioned (p. 116). However, the sodium and potassium alkoxides are relatively insoluble in such inert solvents. Magnesium ethoxide, being soluble in inert solvents,[55,56] offers an advantage in this respect. This base, which readily converts diethyl malonate to its enolate,[57] is of especial value for the dialkylation of this ester.[55,56]

The use of sodium hydride in benzene, toluene, or dimethylformamide is particularly advantageous in alkylation reactions. Sodium hydride reacts irreversibly with an active methylene compound to form an enolate and hydrogen; it has been shown that any sodium hydride which may remain has no effect upon a wide variety of alkyl halides even after prolonged times at elevated temperatures.[58]

Sodium amide is generally used to prepare the sodium derivatives of mononitriles,[53,59] some monocarboxylic esters,[60-62] some alkylmalonic esters, and alkylidenemalonic esters derived from ketones.[63,64] The lithium, sodium, and bromomagnesium salts of secondary amines have found limited use as bases in the alkylation of mononitriles.[53,65,66] The use of lithium diethylamide rather than sodium amide as the base for the alkylation of nitriles avoids side reactions involving addition of the amide ion to the nitrile group (p. 129).[53] This side reaction is particularly serious with disubstituted acetonitriles.

The alkylation of monocarboxylic esters is usually effected in the presence of the strong base sodium triphenylmethide.[67-70] Reactions which employ either sodium amide or sodium triphenylmethide as the base require an inert solvent such as ether, benzene, toluene, or xylene.

Metallic sodium and metallic potassium in inert solvents have been used

[55] Lund, *Ber.*, **67**, 935 (1934).
[56] Lund, Hansen, and Voigt, *Kgl. Danske Videnskab. Selskab, Mat.-fys. Medd.*, **12**, No. 9, 23 (1933) [*C. A.*, **28**, 2333 (1934)].
[57] Walker and Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).
[58] Cristol, Ragsdale, and Meek, *J. Am. Chem. Soc.*, **71**, 1863 (1949).
[59] Ramart, *Compt. Rend.*, **182**, 1226 (1926).
[60] Ramart and Amagat, *Ann. chim. Paris*, [10] **8**, 273 (1927).
[61] Ramart, *Bull. soc. chim. France*, [4] **35**, 196 (1924).
[62] Ramart, *Compt. rend.*, **178**, 396 (1924).
[63] Cope and Hancock, *J. Am. Chem. Soc.*, **60**, 2644 (1938).
[64] Cope, Hofmann, and Hardy, *J. Am. Chem. Soc.*, **63**, 1852 (1941).
[65] Cason, Sumrell, and Mitchell, *J. Org. Chem.*, **15**, 850 (1950).
[66] Ziegler, Fr. pat. 581,728 [*C. A.*, **27**, 4251 (1933)].
[67] Schlenk, Hillemann, and Rodloff, *Ann.*, **487**, 135 (1931).
[68] Hudson and Hauser, *J. Am. Chem. Soc.*, **62**, 2457 (1940).
[69] Hudson and Hauser, *J. Am. Chem. Soc.*, **63**, 3156 (1941).
[70] Polgar and Robinson, *J. Chem. Soc.*, **1943**, 615.

extensively to prepare the enolates of malonic ester, cyanoacetic ester, and 3-aryl-2-benzofuranones. Several attempts to use metallic sodium in the alkylation of aliphatic mononitriles have resulted in dimerization of the nitrile.[71-73] Metallic sodium and metallic potassium must be avoided as bases for the alkylation of alkylidenemalonic and alkylidenecyanoacetic esters because partial reduction of the conjugated system accompanies enolate formation.[28,37,63,74]

Sodium hydroxide and potassium hydroxide have been employed as bases for the alkylation of active methylene compounds. The alkylation of nitriles, in certain instances at least, appears to offer no complications with these bases.[34,75-79] Although extensive saponification would be expected to attend the alkylation of esters in the presence of potassium hydroxide, successful alkylations with this base have been reported by several workers.[80-83] These alkylations were usually effected by treatment of the active methylene compound with a suspension of powdered potassium hydroxide in an inert solvent such as di-n-propyl acetal followed by addition of an alkyl halide. For example, ethyl cyanoacetate was converted to ethyl benzylcyanoacetate in 30% yield by this procedure.[83]

Other bases that have had limited use include benzyltriethylammonium hydroxide,[84] potassium acetate,[85] ammonia,[86,87] potassium carbonate,[88,89] phenylsodium,[90] and various sodium enolates.[91-93] Alkylations have also been effected in the presence of metallic zinc[94] and inorganic salts of

[71] Hanriot and Bouveault, *Bull. soc. chim. France*, [3] 1, 170 (1889).
[72] Wache, *Jahresber.*, 1889, 644.
[73] Holtzwart, *J. prakt. Chem.* [2] 39, 230 (1889).
[74] Hugh and Kon, *J. Chem. Soc.*, 1930, 775.
[75] von Braun, Fussgänger, and Kühn, *Ann.*, 445, 201 (1925).
[76] Zelinsky and Feldmann, *Ber.*, 22, 3290 (1889).
[77] Eisleb, *Ber.*, 74, 1433 (1941).
[78] Cloke, *J. Am. Chem. Soc.*, 51, 1174 (1929).
[79] Pickard and Yates, *J. Chem. Soc.*, 95, 1011 (1909).
[80] Ingold, *J. Chem. Soc.*, 119, 305 (1921).
[81] Weizmann, Bergmann, and Sulzbacher, *J. Org. Chem.*, 15, 918 (1950).
[82] Michael, *J. prakt. Chem.*, [2] 72, 537 (1905).
[83] Weizmann, Brit. pat. 582,191 [*C. A.*, 41, 2436 (1947)].
[84] Jarrousse, *Compt. rend.*, 232, 1424 (1951).
[85] Kohler, Hill, and Bigelow, *J. Am. Chem. Soc.*, 39, 2405 (1917).
[86] Kohler and Conant, *J. Am. Chem. Soc.*, 39, 1404 (1917).
[87] Kötz, *J. prakt. Chem.*, [2] 75, 433 (1907).
[88] Pettersson, *Acta Chem. Scand.*, 4, 1319 (1950) [*C. A.*, 47, 3847 (1953)].
[89] Robinson, *J. Chem. Soc.*, 125, 226 (1924).
[90] Bockmühl and Ehrhardt, Ger. pat. 622,875 [*C. A.*, 30, 2991 (1936)].
[91] Bockmühl and Ehrhaert, *Ann.*, 561, 52 (1948).
[92] Case, *J. Am. Chem. Soc.*, 55, 2927 (1933).
[93] Bockmühl and Ehrhardt, U.S. pat., 2,230,774 [*C. A.*, 35, 3391 (1941)].
[94] Shukowski, *J. Russ. Phys. Chem. Soc.*, 1887 (1), 601; *Ber.*, 21, Ref. 57 (1888).

silver.[95,96]   The yields in several alkylation reactions have been improved when copper or a copper salt was added to the reaction mixture.[97-100]

Monoalkylation versus Dialkylation.   During the alkylation of diethyl sodiomalonate with ethyl bromide, the diethyl ethylmalonate that is

(1) $CH_2(CO_2C_2H_5)_2 + C_2H_5O^{\ominus} \rightleftharpoons \overset{\ominus}{C}H(CO_2C_2H_5)_2 + C_2H_5OH$

(2) $\overset{\ominus}{C}H(CO_2C_2H_5)_2 + C_2H_5Br \rightarrow C_2H_5CH(CO_2C_2H_5)_2 + Br^{\ominus}$

(3) $C_2H_5CH(CO_2C_2H_5)_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightleftharpoons C_2H_5\overset{\ominus}{C}(CO_2C_2H_5)_2$
$$+ CH_2(CO_2C_2H_5)_2$$

(4) $C_2H_5\overset{\ominus}{C}(CO_2C_2H_5)_2 + C_2H_5OH \rightleftharpoons C_2H_5CH(CO_2C_2H_5)_2 + C_2H_5O^{\ominus}$

(5) $C_2H_5\overset{\ominus}{C}(CO_2C_2H_5)_2 + C_2H_5Br \rightarrow (C_2H_5)_2C(CO_2C_2H_5)_2 + Br^{\ominus}$
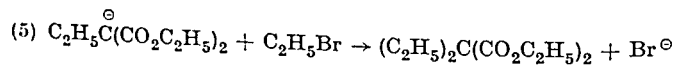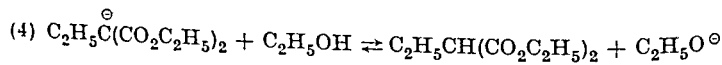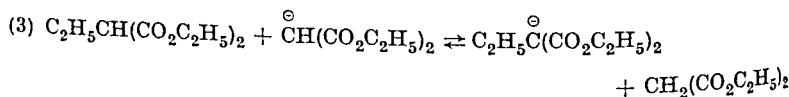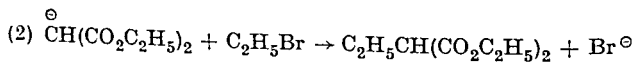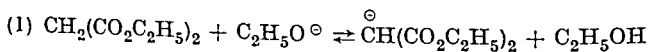
formed (reaction 2) is in equilibrium with its anion (reactions 3 and 4). The question, therefore, arises as to why little dialkylation (reaction 5) is observed.   In a competitive experiment diethyl malonate was alkylated by ethyl bromide (reaction 2) at a rate seventy times the rate of alkylation of diethyl ethylmalonate (reaction 5).[33]   The ratio of the ionization constants[33] of the two esters

$$\frac{K_{\text{diethyl malonate}}}{K_{\text{diethyl ethylmalonate}}} = \frac{1.6 \times 10^{-18}}{2 \times 10^{-20}} \sim 10^2$$

indicates that the concentration of diethyl malonate enolate exceeds the concentration of the diethyl ethylmalonate anion.

Of much greater importance here is the acidity of the solvent, ethanol (K ionization $= 7.28 \times 10^{-20}$).[101]   As can be seen from the enolate-base-solvent equilibria mentioned earlier (p. 110), a solvent that is more acidic than the active methylene compound will greatly reduce the

concentration of enolate present in the reaction mixture since the molar concentration of the solvent is much larger than the molar concentration of the active methylene compound.   In the alkylation of diethyl malonate with ethyl bromide, the presence of a large excess of ethanol in the reaction mixture reduces the concentration of the enolate of diethyl ethylmalonate to such a low level that the rate of dialkylation (reaction 5) becomes negligible.   As would be predicted on this basis, the replacement of ethanol with an inert solvent favors dialkylation.[102]   As would be expected from the facts mentioned above, the greater acidities of alkylcyanoacetic esters and alkylmalonitriles (for malononitrile K ionization $\sim 10^{-11}$)[103] cause dialkylation to be a more serious problem.[95,104–106]

Dialkylation also becomes an important side reaction in the alkylation of active methylene compounds with very reactive halogen compounds such as benzyl halides,[95,107–119] allyl halides,[53,56,120–122] phenacyl halides,[56,106,123,124] and α-chloro thio ethers.[125,126]   The large amount of dialkylation observed with the allyl or benzyl halides or with α-halo ethers may be attributed to the fact that heterolytic cleavage of the carbon-halogen bond in such compounds during bimolecular displacement reactions may occur without substantial aid from the attacking nucleophilic reagent.   Therefore, a halide of this type (e.g., benzyl chloride) would be expected to show less discrimination between two nucleophilic

[102] Clemo and Tenniswood, *J. Chem. Soc.*, **1931**, 2549.

[103] Branch and Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, New York, 1941, p. 269.

[104] Hesse, *Am. Chem. J.*, **18**, 723 (1896).

[105] Cohen, Marshall, and Woodman, *J. Chem. Soc.*, **107**, 887 (1915).

[106] Rây and Rây, *J. Chem. Soc.*, **127**, 2721 (1925).

[107] Bischoff and Siebert, *Ann.*, **239**, 92 (1887).

[108] Fittig and Röders, *Ann.*, **256**, 87 (1890).

[109] Hausmann, *Ber.*, **22**, 2019 (1889).

[110] Poppe, *Ber.*, **23**, 108 (1890).

[111] Cassirer, *Ber.*, **25**, 3018 (1892).

[112] Reissert, *Ber.*, **29**, 633 (1896).

[113] Maxim, *Bull. soc. chim. France*, [4] **39**, 1024 (1926).

[114] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 942 (1935).

[115] Kenner and Witham, *J. Chem. Soc.*, **119**, 1452 (1921).

[116] Walker, *J. Chem. Soc.*, **125**, 1622 (1924).

[117] Gulland, Haworth, Virden, and Callow, *J. Chem. Soc.*, **1929**, 1666.

[118] Curtius and Mülhäusser, *J. prakt. Chem.*, [2] **125**, 291 (1930).

[119] Marvel, *Org. Syntheses*, **21**, 99 (1941).

[120] Paul and Cottin, *Bull. soc. chim. France*, [5] **4**, 933 (1937).

[121] McBay, Jenkins, and Data, *J. Am. Pharm. Assoc.*, **39**, 138 (1950) [C. A., **44**, 4870 (1950)].

[122] Ziegler, Fr. pat. 728,241 [C. A., **26**, 5573 (1932)].

[123] Klobb, *Ann. chim. Paris*, [7] **10**, 168 (1897).

[124] Thorpe, *J. Chem. Soc.*, **91**, 1004 (1907).

[125] Walter, Goodson, and Fosbinder, *J. Am. Chem. Soc.*, **67**, 655 (1945).

[126] Walter, Goodson, and Fosbinder, *J. Am. Chem. Soc.*, **67**, 657 (1945).

reagents (e.g., the sodium enolate of diethyl malonate and the more hindered sodium enolate of diethyl benzylmalonate) than would a saturated alkyl halide (e.g., *n*-butyl chloride; cleavage of the carbon-chlorine bond in this case would be greatly facilitated by the attacking nucleophilic reagent).

In addition to the foregoing suggestion, a second factor may account for the large amount of dialkylation observed with phenacyl halides. A monoalkylated product such as diethyl phenacylmalonate would be expected to be more acidic than a monoalkyl derivative such as diethyl ethylmalonate because of the proximity of an electron-withdrawing carbonyl function in the former example. For this reason the proportion of diethyl phenacylmalonate converted to its sodium enolate, a necessary intermediate for dialkylation, would be larger than the proportion of diethyl ethylmalonate converted to its sodium enolate under comparable conditions.

As the reaction leading to the alkylation of an active methylene compound ($Z—CH_2—Y$) proceeds, the ratio of the concentration of the monosubstituted enolate $[R—\overset{\ominus}{C}(Z)Y]$ to the concentration of the unsubstituted enolate ($Z—\overset{\ominus}{C}H—Y$) must necessarily increase. An increase in this ratio will increase the proportion of dialkylation that occurs. This unfavorable

$$Z—\overset{\ominus}{C}H—Y + R—CH(Z)Y \rightleftarrows Z—CH_2—Y + R—\overset{\ominus}{C}(Z)Y$$
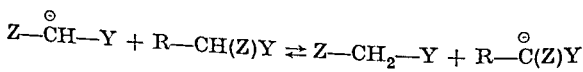
$$\frac{[R—\overset{\ominus}{C}(Z)Y]}{[Z—\overset{\ominus}{C}H—Y]} = \frac{K[R—CH(Z)Y]}{[Z—CH_2—Y]}$$

concentration ratio may be overcome to a large extent if an excess of the active methylene compound ($Z—CH_2—Y$) is used,[7,33,105,116,118,127–135] a possibility first realized by Leuchs.[136] Dialkylation has also been diminished by the addition of an excess of both the active methylene

[127] Gagnon, Boivin, and Boivin, *Can. J. Research*, **28B**, 207 (1950).
[128] Gagnon, Boivin, and Giguère, *Can. J. Research*, **28B**, 352 (1950).
[129] Skinner, *J. Am. Chem. Soc.*, **59**, 322 (1937).
[130] Huber, Clinton, Boehme, and Jackman, *J. Am. Chem. Soc.*, **67**, 1618 (1945).
[131] Gol'mov, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **19**, 1679 (1949) [*C. A.*, **44**, 1030 (1950)].
[132] Olynyk, Camp, Griffith, Woislowski, and Helmkamp, *J. Org. Chem.*, **13**, 465 (1948).
[133] Curtius and Gaier, *J. prakt. Chem.*, [2] **125**, 279 (1930).
[134] Brigl, Hoppe-Seyler's *Z. physiol. Chem.*, **95**, 161 (1915).
[135] Weitzel and Wojahn, Hoppe-Seyler's *Z. physiol. Chem.*, **285**, 220 (1950).
[136] Leuchs, *Ber.*, **44**, 1507 (1911).

compound and the base; such additions serve to increase the concentration

of the active methylene enolate $(Z-\overset{\ominus}{CH}-Y)$.[112,124,137–139]

Other factors reported to favor monoalkylation include the use of low-boiling solvents[53] and the use of alkyl chlorides rather than alkyl bromides.[140]

Order of Introduction of Groups. If two alkyl groups are to be introduced into malonic or cyanoacetic ester, the order of introduction of groups may have a profound influence on the yield and purity of the product. When the two alkyl groups are identical best results have been obtained by adding one equivalent of the base and alkyl halide, allowing the reaction mixture to become approximately neutral, and then adding the second equivalent of base and alkyl halide.[141] Where two different alkyl residues are to be introduced, it is advisable to introduce the larger group first if both alkylation steps involve displacement at a primary carbon atom.[142–145] This order is of particular importance if the smaller alkyl residue is a methyl or an ethyl group; in these cases the boiling points of the unchanged ester, the monoalkylated ester, and the dialkylated ester are too close to one another to permit separation without recourse either to very precise fractional distillation[135] or to a chemical separation (p. 157).

In the dialkylation of malonic ester the introduction of a primary alkyl group should always *precede* the introduction of a secondary alkyl group. If this precaution is not observed the introduction of a second alkyl group is often unsuccessful,[35,145–149] because of the low acidity of the intermediate *sec*-alkylmalonic ester (p. 110) and the sterically hindered nature of the corresponding enolate anion. This difficulty accompanying the alkylation of *sec*-alkylmalonic esters has occasionally been overcome by the use of a strong base such as sodium *t*-butoxide in *t*-butyl alcohol.[35]

Side Reactions. Aside from dialkylation, a wide variety of side reactions may attend the alkylation of an active methylene compound. Among these side reactions are the reactions of the alkylating agent with the base

[137] Hinegardner and Johnson, *J. Am. Chem. Soc.*, **52**, 3724 (1930).
[138] Leveno and Allen, *J. Biol. Chem.*, **27**, 433 (1916).
[139] Zaheer and Sidhu, *J. Indian Chem. Soc.*, **24**, 134 (1947).
[140] Hinegardner and Johnson, *J. Am. Chem. Soc.*, **52**, 4139 (1930).
[141] Leveno and Cretcher, *J. Biol. Chem.*, **33**, 505 (1918).
[142] Dolique, *Ann. chim. Paris*, [10], **15**, 429 (1931).
[143] Dolique, *Compt. rend.*, **190**, 878 (1930).
[144] Dox and Yoder, *J. Am. Chem. Soc.*, **44**, 1141 (1922).
[145] Crossley and Le Sueur, *J. Chem. Soc.*, **77**, 83 (1900).
[146] Kondakova and Katsnel'son, *Compt. rend. acad. sci. (U.R.S.S.) N.S.*, **4**, 403 (1936) [*C. A.*, **31**, 3448 (1937)].
[147] Zelinskii, Bondar, Kost, and Lifshits, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, (1951), No. 2, 96 [*C. A.*, **45**, 10205 (1951)].
[148] Shonle, Keltch, and Swanson, *J. Am. Chem. Soc.*, **52**, 2440 (1930).
[149] Hope and Perkin, *J. Chem. Soc.*, **95**, 1360 (1909).

and solvent. Provided that an adequate concentration of the enolate anion is present (p. 115) the interaction of the alkylating agent and the solvent and/or the base to produce an ether becomes a serious competing reaction only with very reactive halides such as allyl,[150–152] benzyl,[153,154] and benzhydryl halides. The low yields obtained in the synthesis of benzhydrylmalonic esters, presumably attributable to solvolysis of the benzhydryl halides in the alcoholic reaction mixture,[155] may be avoided if the reaction is conducted in benzene solution.[156] Triphenylmethyl chloride also has served as an effective alkylating agent in ether solution.[56]

As was noted earlier (p. 112) tertiary alkyl halides that can undergo dehydrohalogenation usually do so more rapidly than they undergo the displacement reaction leading to alkylation; accordingly, they are poor alkylating agents.[157,159] Olefin formation is less important with secondary alkyl halides[160] and is not a serious side reaction with primary alkyl halides. Halogen compounds like ethyl α-bromoisobutyrate[161–167] and ethyl β-bromolevulinate[168] whose dehydrohalogenation leads to an α,β-unsaturated ester or ketone introduce a further complication; the initially formed unsaturated products may add the active methylene compound in a Michael reaction.[161,162]

$$
\overset{\ominus}{C}H(CO_2C_2H_5)_2 \atop + (CH_3)_2CBrCO_2C_2H_5
$$

$\xrightarrow{\text{Alkylation}}$ $(C_2H_5O_2C)_2CHC(CH_3)_2CO_2C_2H_5$

$\xrightarrow{\text{Dehydrohalogenation}}$ $CH_2=C(CH_3)CO_2C_2H_5$

$CH_2(CO_2C_2H_5)_2 \downarrow$

$(C_2H_5O_2C)_2CHCH_2CH(CH_3)CO_2C_2H_5$
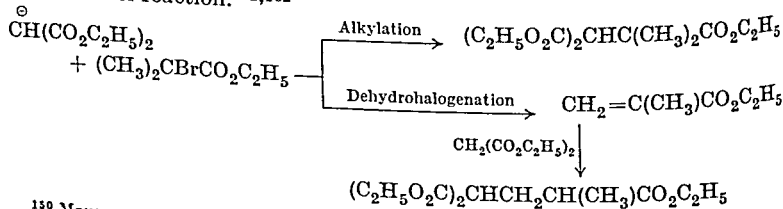
[150] Mousseron and Winternitz, *Bull. soc. chim. France*, 1946, 604.
[151] Perkins and Cruz, *J. Am. Chem. Soc.*, 49, 517 (1927).
[152] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, 1953, 1803.
[153] Mayer, Sieglitz, Fischer, Hagen, Jung, Knies, Kohl, Listmann, Neugebauer, and Schulte, *Ber.*, 55, 1835 (1922).
[154] de Benneville, Clagett, and Connor, *J. Org. Chem.*, 6, 690 (1941).
[155] Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940, p. 167.
[156] Cope, *J. Am. Chem. Soc.*, 56, 721 (1934).
[157] Widegvist, *Arkiv Kemi, Mineral. Geol.*, B23, No. 4, 6 (1946) [*C. A.*, 41, 1615 (1947)].
[158] St. Pfau and Plattner, *Helv. Chim. Acta*, 22, 202 (1939).
[159] Alexander, McCollum, and Paul, *J. Am. Chem. Soc.*, 72, 4791 (1950).
[160] Kazanskii and Lukina, *Doklady Akad. Nauk S.S.S.R.*, 83, 693 (1952) [*C. A.*, 47, 2712 (1953)].
[161] Bischoff and von Kuhlberg, *Ber.*, 23, 634 (1890).
[162] Bischoff and Mintz, *Ber.*, 23, 647 (1890).
[163] Auwers and Jackson, *Ber.*, 23, 1599 (1890).
[164] Zelinsky and Bearedka, *Ber.*, 24, 459 (1891).
[165] Bischoff, *Ber.*, 24, 1041 (1891).
[166] Auwers and Kobner, *Ber.*, 24, 1923 (1891).
[167] Bone and Sprankling, *J. Chem. Soc.*, 75, 839 (1899).
[168] Emery, *J. prakt. Chem.*, [2] 53, 308 (1896).

Decarbalkoxylation (p. 127) and side reactions which involve the alkylating agent and the base may be minimized if a mixture of the alkylating agent and the active methylene compound is treated with the base at a rate equal to that at which the base is consumed in the reaction.[42,121,169,170]

Similarly, the slow addition of the sodium derivatives of mononitriles to allylic halides has been found to minimize the extent of polymerization of both the alkylating agent and the product.[171]

Certain vicinal dihalides tend to lose their halogen atoms with the simultaneous production of the corresponding olefin under the conditions of the alkylation reaction. Such dihalides include ethylene iodide (but not ethylene bromide),[92] 2,3-dibromo-2-methylbutane,[172,173] o,o'-dinitrostilbene dibromide,[174] and diethyl $erythro$-α,α'-dibromosuccinate.[175] For each molecule of halogen lost, two molecules of the active methylene compound are coupled in a reaction similar to the coupling of active methylene compounds in the presence of iodine (p. 137). Certain of the olefins produced in this way may add an additional equivalent of the active methylene compound in a Michael reaction.[175] The reaction of
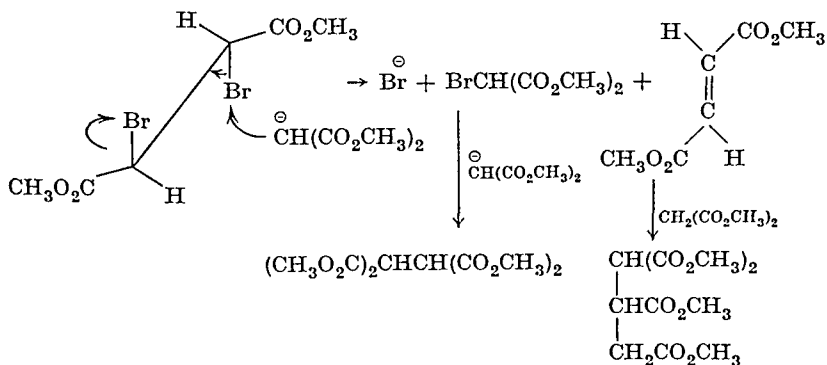
dimethyl $erythro$-α,α'-dibromosuccinate is illustrative. In addition to the major products, dimethyl fumarate, tetramethyl 1,1,2,2-ethanetetracarboxylate, and tetramethyl 1,1,2,3-propanetetracarboxylate, a small amount of racemic tetramethyl 1,1,2,3-cyclopropanetetracarboxylate was formed. The cyclopropane tetracarboxylic ester is believed to arise from

[169] Phillips, *Ind. Chemist*, **21**, 678 (1945).
[170] Mariella and Raube, *Org. Syntheses*, **33**, 23 (1953).
[171] Whyte and Cope, *J. Am. Chem. Soc.*, **65**, 1999 (1943).
[172] Bischoff, *Ber.*, **28**, 2824 (1895).
[173] Ipatiew, *J. Russ. Phys. Chem. Soc.*, **30**, 391 (1898) (*Chem. Zentr.*, 1898, II, 660).
[174] Bischoff, *Ber.*, **21**, 2071 (1888).
[175] Ing and Perkin, *J. Chem. Soc.*, **125**, 1814 (1924).

the partial base-catalyzed isomerization of the dimethyl *erythro*-α,α'-dibromosuccinate to the *threo* isomer; dimethyl *threo*-α,α'-dibromosuccinate, when treated with dimethyl sodiomalonate, was converted to
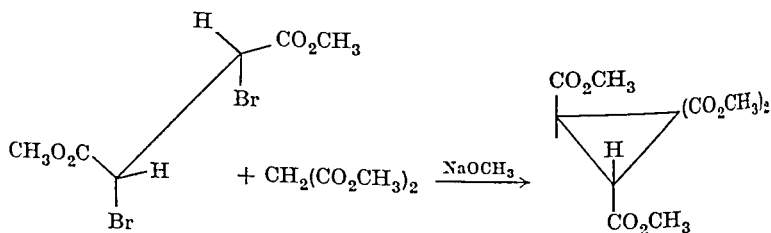
the racemic cyclopropane tetracarboxylic ester in 80–90% yield.[175] A similar base-catalyzed epimerization of the isomeric α,α'-dibromoglutaric esters has been observed.[176]

Another side reaction which involves the transfer of a halogen atom is exemplified by the attempted alkylation of methyl diphenylacetate with methyl α-bromophenylacetate in the presence of sodium triphenylmethide.[67] The product was dimethyl α,α'-diphenylsuccinate.

$$(C_6H_5)_3C^\ominus + C_6H_5CHBrCO_2CH_3 \rightarrow (C_6H_5)_3CBr + C_6H_5\overset{\ominus}{C}HCO_2CH_3$$

$$C_6H_5\overset{\ominus}{C}HCO_2CH_3 + C_6H_5CHBrCO_2CH_3 \rightarrow Br^\ominus$$
$$+ CH_3O_2CCH(C_6H_5)CH(C_6H_5)CO_2CH_3$$
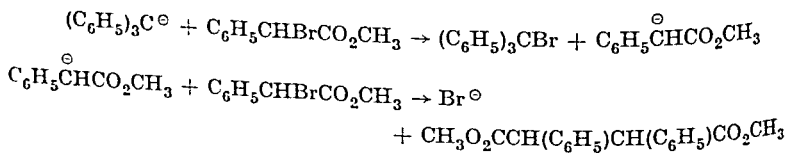
Similarly, 2-bromo-2-nitropropane and diethyl sodiomalonate underwent partial halogen interchange, the products being tetraethyl 1,1,2,2-ethanetetracarboxylate and 2,3-dimethyl-2,3-dinitrobutane.[177] However, normal alkylation was observed when 2-chloro-2-nitropropane was allowed to react with the sodium enolate of diethyl ethylmalonate.[177] Halogenated nitroalkanes in which the nitro group is bonded to a carbon atom

$$(CH_3)_2C(NO_2)Br + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} (CH_3)_2C(NO_2)C(NO_2)(CH_3)_2$$
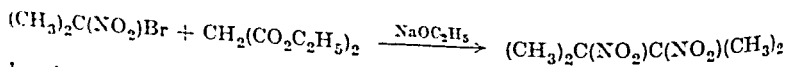
bearing a hydrogen atom cannot be employed as alkylating agents. Instead, the enolate of the nitro compound is formed, since it is less basic than the enolate of malonic ester.

In addition to the side reactions that can occur with the alkylating agent, both the initial active methylene compound and the alkylated product can undergo a number of transformations. The possibility of ester interchange when the alkoxyl group of the ester and the alkoxide ion differ has already been mentioned (p. 117). When sodium amide is

[175] Ingold and Perkin, *J. Chem. Soc.*, **127**, 2387 (1925).
[177] Van Tamelen and Van Zyl, *J. Am. Chem. Soc.*, **71**, 835 (1949).

used as the base for the alkylation of esters, amide formation may be a serious side reaction.[178,179]

$$C_6H_5CH_2CO_2C_2H_5 + H_2N^\ominus \rightleftharpoons C_6H_5CH_2\underset{\underset{NH_2}{\big|}}{\overset{\overset{OC_2H_5}{\big|}}{C}}-O^\ominus \rightleftharpoons C_6H_5CH_2CONH_2 + C_2H_5O^\ominus$$
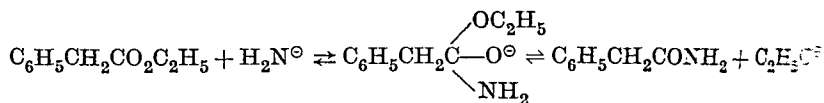
A related side reaction results in the loss of the carbalkoxyl group as the corresponding dialkyl carbonate.[180] Similarly, cyanoacetic esters are converted to mononitriles.[181] Among the malonic esters the importance

$$C_6H_5CH(CO_2C_2H_5)_2 \underset{\xrightarrow{\hspace{1cm}}}{\overset{C_2H_5O^\ominus}{\xleftarrow{\hspace{1cm}}}} C_6H_5CH(CO_2C_2H_5)\underset{\underset{OC_2H_5}{\big|}}{\overset{\overset{OC_2H_5}{\big|}}{C}}-O^\ominus \rightleftharpoons$$

$$C_6H_5\overset{\ominus}{C}HCO_2C_2H_5 + (C_2H_5O)_2CO$$

$$\text{indanyl}-C(CH_3)(CN)CO_2C_2H_5 + C_2H_5O^\ominus \rightleftharpoons$$

$$\text{indanyl}-\overset{\ominus}{C}(CH_3)CN + (C_2H_5O)_2CO$$
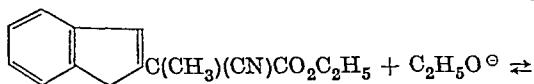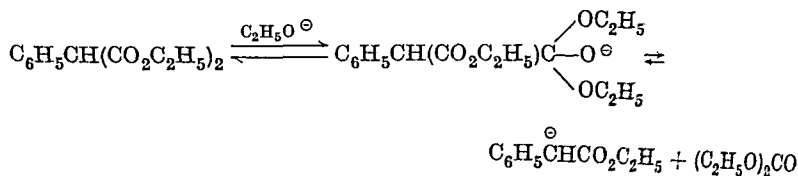
of this side reaction decreases in the following order: diethyl diphenyl-malonate > diethyl ethyl(phenyl)malonate > diethyl diethylmalonate.[182]

$$(C_6H_5)_2C(CO_2C_2H_5)\underset{\underset{OC_2H_5}{\big|}}{\overset{\overset{OC_2H_5}{\big|}}{C}}-O^\ominus \rightarrow (C_2H_5O)_2CO +$$
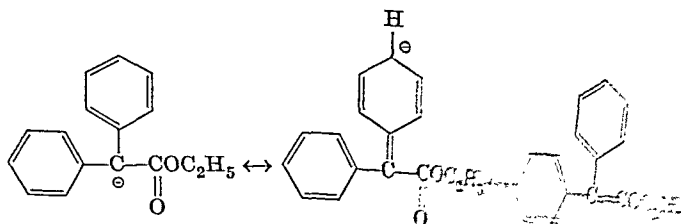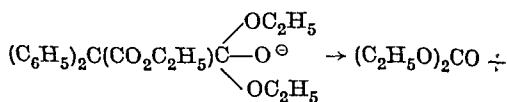
Such an order is understandable when the resonance stabilization available to the carbanion formed after loss of diethyl carbonate is considered. Substituents other than the phenyl group[180,182] which have been observed to enhance the cleavage reaction include the nitro group,[183] the vinyl group,[54] the 2,4-dinitrophenyl group,[184] and the 2- or 3-indenyl group.[181] On the other hand, bulky groups that impede the approach of the ethoxide ion or substituents that reduce the stability of a carbanion diminish the amount of decarbethoxylation. Malonic esters and monoalkylmalonic esters are less readily cleaved to monocarboxylic esters and dialkyl carbonates because they react readily with sodium alkoxides to form stable enolates.

The reversible nature of the decarbethoxylation of diethyl phenylmalonate has been demonstrated.[43] In fact, the reverse reaction, carbethoxylation, has been found valuable both in the synthesis of diethyl phenylmalonate from ethyl phenylacetate and in the synthesis of cyanoacetic esters from mononitriles.[185–189] As mentioned previously (p. 117), the use of diethyl carbonate as a solvent for the alkylation reaction offers special advantages where cleavage might be an important side reaction. The extent of decarbethoxylation is diminished and the reaction time is shortened by virtue of the high boiling point of the diethyl carbonate.

The decarbethoxylation of disubstituted malonic esters at high temperatures in the presence of ethanol-free sodium ethoxide or sodium or potassium metal (p. 150) would constitute a serious side reaction where the alkylation of an alkylmalonic ester was attempted under such conditions.

In the alkylation of malononitriles (see Table X), the addition of ethanol to one of the cyano groups to produce stable imido esters is often observed.[95,104] The mononitriles are usually stable to ethanolic sodium

$$C_6H_5CH_2CH(CN)_2 + CH_3I + C_2H_5OH \xrightarrow{NaOC_2H_5}$$
$$C_6H_5CH_2C(CH_3)(CN)\underset{\underset{NH}{\parallel}}{C}OC_2H_5$$
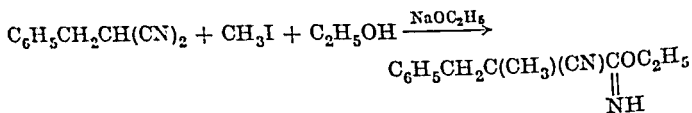
ethoxide, 4-cyano-1-methyl-4-phenylpiperidine being an exception;[190] an imido ester presumably is an intermediate in the cleavage. The stronger

base, sodium amide, does attack the cyano group in such solvents as boiling benzene,[191] toluene,[192] or xylene.[191–194]   Under such conditions

$$H_3CN \underset{C\equiv N}{\overset{C_6H_5}{\diagdown}} \xrightarrow{C_2H_5OH,\ NaOC_2H_5} H_3CN \underset{}{\diagdown} C_6H_5$$

86%
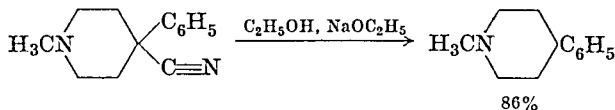
the nitrile function may be eliminated as sodium cyanamide.

$$(C_6H_5)_2C(CN)CH_2CH_2N(CH_3)_2 + 2NaNH_2 \xrightarrow{Xylene}$$
$$NH_3 + Na_2N_2C + (C_6H_5)_2CHCH_2CH_2N(CH_3)_2$$
91%
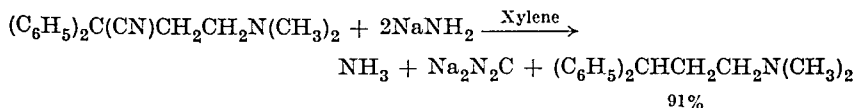
The loss of the nitrile function has also been observed with substituted nitriles which have no hydrogen atom on the carbon atom *alpha* to the nitrile group and which have a hydrogen atom and a phenyl group on the carbon atom *beta* to the cyano group.[195]   This elimination of hydrogen cyanide may be likened to other bimolecular elimination processes as is shown in the accompanying equation.   In the presence of basic catalysts

$$C_6H_5CH\overset{H}{\underset{\underset{CN}{|}}{-}}C(C_6H_5)_2 \rightarrow C_6H_5CH{=}C(C_6H_5)_2 + NH_3 + CN^{\ominus}$$
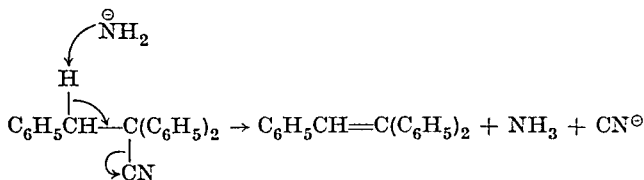
both acetic esters and mono- and di-substituted acetic esters can condense with themselves in a reaction of the acetoacetic ester type[179] to produce β-keto esters with a consequent diminished yield of the alkylated product.[178,196]   A similar condensation, the Thorpe reaction, occurs as a side reaction and results in poor yields in the alkylation of certain mononitriles.[71–73]   Such Claisen-type condensations become particularly important with compounds where intramolecular condensation is possible.[176,197–201]   The accompanying example[198] illustrates both a

[191] Ruddy, *J. Am. Chem. Soc.*, **73**, 4096 (1951).
[192] Jackman, Nachod, and Archer, *J. Am. Chem. Soc.*, **72**, 716 (1950).
[193] Jackman, Bolen, Nachod, Tullar, and Archer, *J. Am. Chem. Soc.*, **71**, 2301 (1949).
[194] Kleiderer, *Report No. P.B. 981*, Office of the Publication Board, Dept. of Commerce, Washington, D.C.
[195] Hauser and Brasen, to be published.
[196] Scheibler, Marhenkel, and Bassanoff, *Ber.*, **58**, 1198 (1925).
[197] Perkin and Thorpe, *J. Chem. Soc.*, **79**, 729 (1901).
[198] Mitchell and Thorpe, *J. Chem. Soc.*, **97**, 2261 (1910).
[199] Goss and Ingold, *J. Chem. Soc.*, **1928**, 1268.
[200] Acheson and Robinson, *J. Chem. Soc.*, **1952**, 1127.
[201] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, **1953**, 1799.

Claisen condensation and the subsequent elimination of a carbethoxyl group.
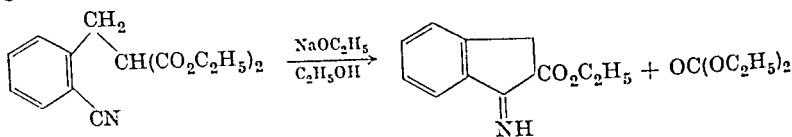
Active methylene compounds having alkoxyl[202-204] or alkylthio[205] functions bonded to the carbon atom *beta* to the activating group have been observed to undergo base-catalyzed elimination under the conditions of the alkylation reaction. The unsaturated compounds initially formed are susceptible to polymerization and Michael reactions.
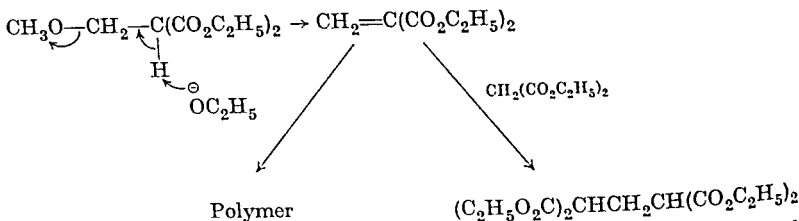
During the alkylation of certain malonic esters a reverse Michael reaction competes with the alkylation reaction. In such cases the alkylation products of diethyl malonate or diethyl monoalkylmalonates are isolated.[87,154,206,207] For example, the products of the alkylation of ethyl γ-benzoyl-α-carbethoxy-β-phenylbutyrate (I) were dependent on the alkylating agent employed.[154] With methyl iodide both the keto
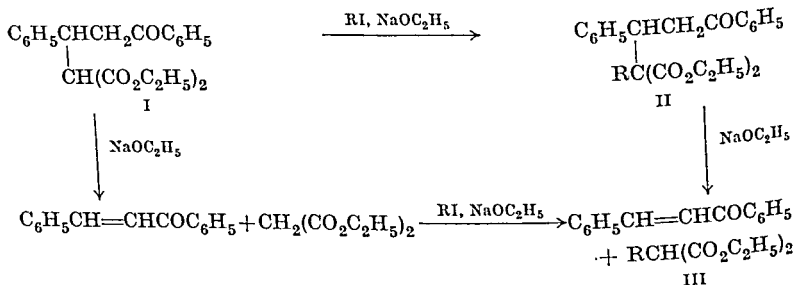
[202] Ziegler, Schenck, Krockow, Siebert, Wenz, and Weber, *Ann.*, **551**, 1 (1942).

[203] McElvain and Burkett, *J. Am. Chem. Soc.*, **64**, 1831 (1942).

[204] Simonsen, *J. Chem. Soc.*, **93**, 1777 (1908).

[205] Böhme and Greve, *Chem. Ber.*, **85**, 409 (1952).

[206] Perkin, *J. Chem. Soc.*, **69**, 1500 (1896).

[207] Rydon, *J. Chem. Soc.*, **1935**, 420.

ester II (R = CH_3) and diethyl methylmalonate (III, R = CH_3) were formed. If the less reactive ethyl iodide was employed, only diethyl ethylmalonate (III, R = C_2H_5) was produced since the reaction mixture remained basic sufficiently long for the reverse Michael reaction to predominate. Whether the cleavage occurred before or after the alkylation step is not known.

If the active methylene compound employed contains other reactive functions additional side reactions are possible. In the case of diethyl chloromalonate the rate of displacement of the chloride ion by the ethoxide anion exceeds the rate of alkylation except with very reactive alkylating agents such as benzyl chloride[208] or 4-(or 5-)chloromethylimidazole.[209] Small amounts (1.5%) of diethyl 5-ethoxyhexylmalonate were formed along with diethyl 2-methylcyclohexane-1,1-dicarboxylate when diethyl 5-bromohexylmalonate was cyclized in the presence of sodium ethoxide.[210]

Additional side reactions may accompany the alkylation of alkylidene-malonic esters, alkylidenecyanoacetic esters, and alkylidenemalononitriles. These include polymerization[28,37,211,212] and reverse aldol reactions.[28] If sodium in an inert solvent is used to prepare the enolates of alkylidene esters partial reduction may occur (p. 119).

The products obtained from the alkylation of alkylidene derivatives of malonic ester,[64,213] cyanoacetic ester,[64,214-217] malononitriles,[215,216] and mononitriles[171] with allylic halides have been found to undergo thermal isomerization in certain cases, and the products must be distilled at temperatures that do not cause rearrangement. For the various active methylene compounds used, the rates of such rearrangements fall in the order: malononitriles > cyanoacetic esters > malonic esters.[171,213,215,216]

$$CH_2{=}C{-}CH_3$$
$$\diagdown$$
$$\qquad C(CO_2C_2H_5)_2 \xrightarrow{\ 185° \ } CH_2{-}CCH_3$$
$$\diagup \qquad\qquad\qquad\qquad \|$$
$$CH_3CH{=}CHCH_2 \qquad\qquad\qquad C(CO_2C_2H_5)_2$$
$$CH_3CH{-}CH{=}CH_2$$
$$90\%$$
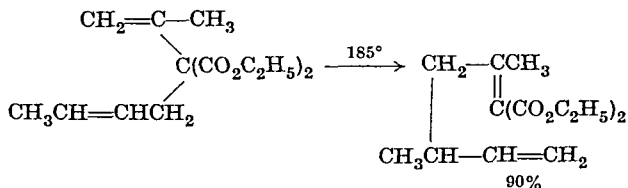
Steric effects influence markedly the ease of these rearrangements.[213,215]

[208] Conrad, *Ann.*, **209**, 241 (1881).

[209] Pyman, *J. Chem. Soc.*, **99**, 1386 (1911).

[210] Gol'mov, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **23**, 1162 (1953) [*C. A.*, **47**, 12255 (1953)].

[211] Cope and Hoyle, *J. Am. Chem. Soc.*, **63**, 733 (1941).

[212] Cope, U.S. pat. 2,222,455 [*C. A.*, **35**, 1802 (1941)].

[213] Aldridge and Murphy, *J. Am. Chem. Soc.*, **73**, 1158 (1951).

[214] Cope and Hardy, *J. Am. Chem. Soc.*, **62**, 441 (1940).

[215] Cope, Hoyle, and Heyl, *J. Am. Chem. Soc.*, **63**, 1843 (1941).

[216] Foster, Cope, and Daniels, *J. Am. Chem. Soc.*, **69**, 1893 (1947).

[217] Cope and Field, *J. Am. Chem. Soc.*, **71**, 1589 (1949).

The Active Methylene Compound

Malonic Esters (Table I). In the many alkylations reported to yield monoalkylmalonic esters, the base-solvent combination generally employed was sodium ethoxide in ethanol. As noted previously (p. 120) such reaction conditions inhibit dialkylation since, in most cases, the monoalkyl derivative is less acidic than ethanol. This advantage, which is not shared with cyanoacetic ester and malononitrile, recommends malonic ester if only the monoalkyl compound is desired. The separation problem that arises in the preparation of methylmalonic esters and ethylmalonic esters (p. 123) is best avoided by employing an alternative synthetic method (p. 147) for these esters. The use of the ethoxymagnesium salt of malonic ester rather than sodiomalonic ester is a valuable modification[55,56,150,218-220] if the alkylation is to be run in an inert solvent such as ether or benzene (p. 116). Diethyl carbonate (pp. 117, 128) offers advantages as the solvent in some instances.

Substituted Malonic Esters (Tables II, III, and IV) and Alkylidenemalonic Esters (Table V). The reduced acidity[5] of monoalkylmalonic esters (p. 110) in which the alkyl group is secondary or tertiary[44,52,145-149,221-226] has resulted in low yields during alkylations in the presence of ethanolic sodium ethoxide. This difficulty, which is much less serious with the analogous cyanoacetic esters (p. 134), has been overcome by recourse to stronger bases and less acidic solvents. The use of sodium t-butoxide in t-butyl alcohol has permitted the alkylation of diethyl isopropylmalonate,[35] diethyl (1-ethylbutyl)malonate,[35] and diethyl cyclohexylmalonate.[35] Diethyl diisopropylmalonate was prepared by the use of sodium and ether at elevated temperatures in a sealed tube.[52] Diethyl ethyl-(sec-butyl)malonate was obtained in 95% yield when the ethanol-free sodium enolate of diethyl sec-butylmalonate was heated with ethyl bromide in diethyl carbonate.[44,51,227] Another striking demonstration of the value of this method is found in the alkylation of diethyl t-butylmalonate with allyl bromide, the reaction being effected in 36% yield in the presence of sodium ethoxide and diethyl carbonate.[44] Benzene and toluene have

[218] Fuson and Jackson, J. Am. Chem. Soc., **72**, 351 (1950).
[219] Ali-Zade and Arbuzov, Zhur. Obshchei Khim. (J. Gen. Chem. U.S.S.R.), **13**, 113 (1943) [C. A., **38**, 352 (1944)].
[220] Terent'ev, J. Russ. Phys.-Chem. Soc., **60**, 85 (1928) [C. A., **22**, 3880 (1928)].
[221] Conrad and Guthzeit, Ann., **222**, 249 (1883).
[222] Fischer and Dilthey, Ann., **335**, 334 (1904).
[223] Bischoff, Ber., **29**, 972 (1896).
[224] Cope and Lyman, J. Am. Chem. Soc., **75**, 3312 (1953).
[225] Marshall, J. Chem. Soc., **1930**, 2754.
[226] Weizmann, Sulzbacher, and Bergmann, J. Chem. Soc., **1947**, 772.
[227] Wallingford and Homeyer, U.S. pat. 2,391,530 [C. A., **40**, 3770 (1946)].

served as solvents for the alkylation of the sodium salts of diethyl benz-hydrylmalonate[156] and dibenzhydryl benzhydrylmalonate[224] with benz-hydryl bromide.

The introduction of a phenyl group reduces the acidity of diethyl malonate or ethyl phenylacetate, the reduction in acidity being comparable with that resulting from the introduction of a methyl group (p. 110).[5] An explanation for this phenomenon may be the non-coplanarity of the phenyl derivative, which inhibits effective resonance stabilization of the enolate anion.

Alkylation of chloromalonic ester is successful only with very reactive alkylating agents (p. 131).[209,228-230] With less reactive alkylating agents, coupling of the malonic ester residues[231] or ether formation is the predominant reaction. In the alkylation of nitromalonic ester, the alkyl group is introduced on the carbon atom[183] rather than on an oxygen atom. Whereas the alkylation of aminomalonic esters results in both C- and N-alkylation,[232] formamido, acetamido, benzamido, and phthalimido derivatives of malonic ester can be alkylated without N-alkylation. The formamido- and acetamido-malonates are most useful since the phthalimido derivatives are hydrolyzed and decarboxylated with difficulty[233] and many of the alkyl(benzamido)malonic esters are oils.[232] The facile deacylation of formamidomalonates and acetamidomalonates may be disadvantageous if the alkylation reaction is slow. The yields of the isopropyl derivative obtained with diethyl acetamidomalonate (37%)[234,235] and with diethyl benzamidomalonate (66%)[233] are explicable in terms of the greater susceptibility of the acetamido group to alcoholysis. The absence of alcohol in the reaction mixture has proved advantageous in the alkylation of diethyl phthalimidomalonate with 1,3-dibromopropane and with γ-phthalimidopropyl bromide.[236]

The alkylation of alkylidenemalonic esters produces the α-alkyl derivative of the corresponding β,γ-unsaturated ester. The accompanying

$$CH_3CH_2C(CH_3){=}C(CO_2C_2H_5)_2 + n\text{-}C_3H_7Br \xrightarrow{\ NaNH_2\ }$$
$$CH_3CH{=}C(CH_3)C(n\text{-}C_3H_7)(CO_2C_2H_5)_2$$
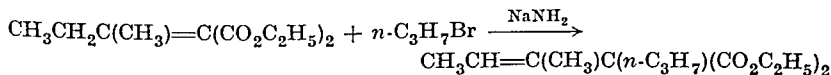
example[237] illustrates the shift of the double bond to yield the more highly

[228] Perkin, *J. Chem. Soc.*, **53**, 1 (1888).

[229] Kipping, *J. Chem. Soc.*, **53**, 21 (1888).

[230] Titley, *J. Chem. Soc.*, **1928**, 2571.

[231] Kötz and Zörnig, *J. prakt. Chem.*, [2] **74**, 425 (1906).

[232] Albertson, *J. Am. Chem. Soc.*, **68**, 450 (1946).

[233] Redemann and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

[234] Atkinson and Scott, *J. Chem. Soc.*, **1949**, 1040.

[235] Snyder, Shekleton, and Lewis, *J. Am. Chem. Soc.*, **67**, 310 (1945).

[236] Sörensen, *Hoppe-Seyler's Z. physiol. Chem.*, **44**, 448 (1905).

[237] Cope and Hancock, *J. Am. Chem. Soc.*, **60**, 2901 (1938).

substituted vinyl derivative, which occurs when the double bond can migrate into either of two positions. As with saturated alkylmalonic ester derivatives, chain branching markedly reduces the acidity of alkylidenemalonic esters. Although sodium ethoxide may serve as the base for the alkylation of alkylidenemalonic esters derived from aldehydes,[28] the branched alkylidene derivatives prepared from ketones require a stronger base.[237] Since the use of sodium in an inert solvent causes reduction of the alkylidene derivative (p. 119), sodium amide in liquid ammonia or in an inert solvent has proved to be most satisfactory for the preparation of enolates from alkylidenemalonic esters derived from ketones.

Cyanoacetic Esters (Table VI). Like malonic esters, cyanoacetic esters are usually alkylated in the presence of ethanolic sodium ethoxide. The increased importance of dialkylation (p. 121) as a side reaction attending the alkylation of cyanoacetic esters has been discussed. The high order of reactivity of the ethyl cyanoacetate enolate has been utilized advantageously to prevent side reactions with very reactive alkylating agents;[238] in such cases reaction of the alkylating agent with the enolate anion is apparently more rapid than the reaction of the alkylating agent with the base or the solvent.

Substituted Cyanoacetic Esters (Tables VII and VIII) and Alkylidenecyanoacetic Esters (Table IX). The use of cyanoacetic esters rather than malonic esters is recommended if the preparation of a dialkyl derivative is desired. Monoalkyl derivatives of cyanoacetic ester are readily alkylated in the presence of ethanol and sodium ethoxide even if the first alkyl group introduced is branched.[145,225,226,238–240] This property both simplifies the preparation of dialkylcyanoacetic esters and eliminates the need to introduce the primary alkyl group in the first stage of the alkylation as often must be done with malonic esters (p. 123). For example, ethyl ethyl(isopropyl)cyanoacetate was prepared in 86% yield from ethyl isopropylcyanoacetate and ethyl iodide,[239] whereas diethyl ethyl(isopropyl)malonate was obtained from diethyl isopropylmalonate under similar conditions in very poor yield.[145]

Ethyl acetamidocyanoacetate[232,241,242] and methyl (phenylacetamido)-cyanoacetate[243–245] have been alkylated in the presence of alcoholic

[238] Tabern and Volwiler, J. Am. Chem. Soc., 56, 1139 (1934).
[239] Fischer, Rohde, and Brauns, Ann., 402, 364 (1914).
[240] Fischer and Flatau, Ber., 42, 2981 (1909).
[241] Albertson and Tullar, J. Am. Chem. Soc., 67, 502 (1945).
[242] Fields, Walz, and Rothchild, J. Am. Chem. Soc., 73, 1000 (1951).
[243] Ehrhart, Chem. Ber., 82, 60 (1949).
[244] Ehrhart, Chem. Ber., 82, 387 (1949).
[245] Horner and Medem, Chem. Ber., 85, 520 (1952).

sodium alkoxides without difficulty. Sodium hydride has been recommended as the base for the alkylation of acetamidomalonic ester and acetamidocyanoacetic ester.[246]

The alkylation of alkylidenecyanoacetic esters derived from aldehydes has failed because these alkylidene derivatives are rapidly polymerized in the presence of bases.[212] Aside from the fact that only the alkylidenemalonic esters derived from the simplest ketones are available,[37,74] the use of alkylidenecyanoacetic esters derived from ketones rather than the malonic ester analogs offers an advantage in that the cyanoacetate derivatives may be alkylated in the presence of ethanolic sodium ethoxide.[37] However, sodium isopropoxide in isopropyl alcohol has been recommended for the alkylation of secondary alkylidenecyanoacetic esters.[37,211,247]

Malononitriles (Table X) and Alkylidenemalononitriles (Table IX). Malononitrile, monoalkylmalononitriles, and alkylidenemalononitriles have been alkylated in the presence of ethanolic sodium ethoxide. However, the usefulness of the reaction is often limited by the simultaneous addition of the alcohol to one of the nitrile groups of the product[95,104,211] to produce an imido ester (p. 128). In addition the alkylidenemalononitriles derived from aldehydes polymerize very readily.[211] The use of malononitrile to form monoalkyl derivatives is limited by the ease with which it is dialkylated.[95]

Monocarboxylic Esters (Table XI), 3-Aryl-2-benzofuranones (Table XII), and Succinic, Glutaric and Glutaconic Esters (Table XIII). Either sodium amide or sodium triphenylmethide in an inert solvent is the base most often used to produce the enolates of monocarboxylic esters. These sodium enolates have been alkylated with alkyl and allyl halides, with dihalogenated alkanes,[248] with phenacyl bromide,[248] with nitroaryl halides,[248] with 4,7-dichloroquinoline,[178] with epoxides,[69] with dialkyl sulfates,[249] and with alkyl sulfonates.[69] In contrast to the mononitriles (p. 136), dialkylation is not a serious problem. The 3-aryl-2-benzofuranones most often have been alkylated by treatment with sodium or potassium metal in an inert solvent followed by treatment with an alkylating agent. Several α-bromoglutaric esters have been converted to the corresponding cyclopropane derivatives by self-alkylation, the base used being sodium carbonate or potassium hydroxide.[80,250]

As cited previously (p. 110), the acidity of acetic esters is reduced by alkyl substitution especially if the alkyl group is branched.[5] Although the acidity of ethyl acetate is enhanced by the substitution of one phenyl group

[246] Shapira, Shapira, and Dittmer, *J. Am. Chem. Soc.*, **75**, 3655 (1953).

[247] Mitter and Dutta, *J. Indian Chem. Soc.*, **25**, 306 (1948).

[248] Wislicenus and Mocker, *Ber.*, **46**, 2772 (1913).

[249] Bowden, *J. Am. Chem. Soc.*, **60**, 131 (1938).

[250] Perkin and Thorpe, *J. Chem. Soc.*, **75**, 48 (1899).

of the base potassium amide in a mixture of liquid ammonia and ether as the solvent has proved advantageous for the alkylation of phenylaceto-nitrile and diphenylacetonitrile.[195] The alkylating agents employed include alkyl and allyl halides, dihalogenated alkanes, chloropyridines, chloroquinolines, epoxides, dialkyl sulfates, and alkyl sulfonates. In some instances elevated reaction temperatures favor dialkylation,[53] elimination of the cyano group,[91,191-193] or dimerization of the nitrile.[71-73] When 2- or 4-chloropyridines or 4-chloroquinolines were employed as the alkylating agent for phenylacetonitrile the yield of product did not exceed 50% unless two equivalents of sodium amide were used.[178,254] This result has been attributed to the formation of an insoluble sodium salt which removed an additional equivalent of base from the reaction mixture.[178]

The metal salts of primary and secondary amines have been used as bases for the alkylation of mononitriles.[53,66,255] Sodium hydroxide and potassium hydroxide have also served as bases for the alkylation of nitriles.[34,75-79,256,257]
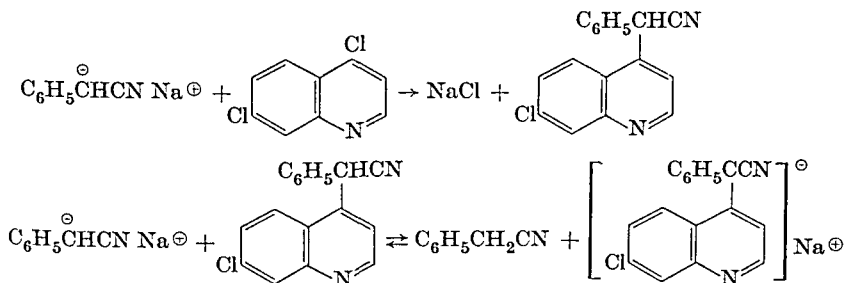
Aldehydes[258,259] and ketones[171,193,259] condense readily with mono-nitriles. The alkylidene derivatives formed from ketones are best con-verted to their sodium enolates with sodium amide. Thus the alkylation of cyclohexylidene(phenyl)acetonitrile failed in ethanolic sodium ethoxide;[259] with the stronger base sodium amide in benzene or ether, alkylated products were obtained in yields of 77-82%.[171]

Alkylating Agents

Halogens. The addition of bromine or iodine to an enolate often results in the coupling of two molecules of the active methylene compound. The

[254] Sperber, Papa, Schwenk, Sherlock, and Fricano, *J. Am. Chem. Soc.*, **73**, 5752 (1951).

[255] Ziegler, Ger. pat. 583,561 [*C. A.*, **28**, 1057 (1934)].

[256] Meyer, *Ann.*, **250**, 118 (1888).

[257] Haller and Benoist, *Ann. chim. Paris*, [9] **17**, 25 (1922).

[258] Murray and Cloke, *J. Am. Chem. Soc.*, **58**, 2014 (1936).

[259] McRae and Manske, *J. Chem. Soc.*, **1928**, 484.

probable course of the reaction[107,260,261] will be seen to resemble the course of an analogous side reaction involving vicinal dihalides (p. 125). Similar dimeric products have been formed from monocarboxylic esters,[67,69,248] 3-aryl-2-benzo-furanones,[262,263] and mononitriles.[264] However, the enolates of some monosubstituted malonic esters formed only the iodinated derivative of the active methylene compound when treated with iodine.[265] That monosubstitution need not always inhibit this coupling reaction is indicated by the treatment of various polymethylene-α,ω-dimalonic esters with iodine and a base; the corresponding carbocycles are formed.[87,266–269]

$$C_2H_5CH[CH(CO_2C_2H_5)_2]_2 + 2NaOC_2H_5 + I_2 \rightarrow$$

$$H_5C_2CH \diagup \begin{matrix} C(CO_2C_2H_5)_2 \\ | \\ C(CO_2C_2H_5)_2 \end{matrix} + 2NaI + 2C_2H_5OH$$
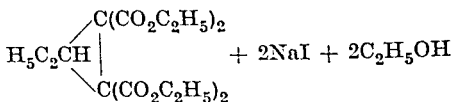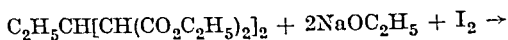
When the sodium enolate of ethyl cyanoacetate is treated with iodine a cyclic trimer is formed;[270–272] the same product results when ethyl bromocyanoacetate is heated with aniline in ether.[273]

$$CH_2(CN)CO_2C_2H_5 \xrightarrow[I_2]{NaOC_2H_5}$$
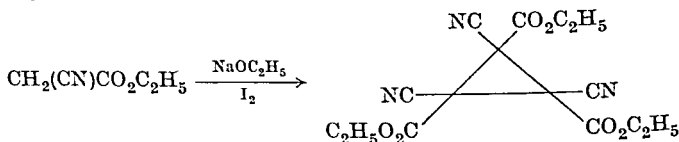
Alkyl Halides. In reactivity as alkylating agents for active methylene compounds the various halogenated organic compounds lie in the order observed for other bimolecular nucleophilic displacement reactions; the allyl and benzyl halides are more reactive than the alkyl halides,[274] which in turn are more reactive than the vinyl[54,275–277] and aryl[142,278] halides.

[260] Bischoff and Rach, *Ber.,* **17,** 2781 (1884).
[261] Lennon and Perkin, *J. Chem. Soc.,* **1928,** 1513.
[262] Löwenbein and Simonis, *Ber.,* **57,** 2040 (1924).
[263] Löwenbein, *Ber.,* **58,** 601 (1925).
[264] Auwers and Meyer, *Ber.,* **22,** 1227 (1889).
[265] Bischoff and Hausdörfer, *Ann.,* **239,** 110 (1887).
[266] Perkin, *J. Chem. Soc.,* **51,** 1 (1887).
[267] Perkin, *J. Chem. Soc.,* **51,** 240 (1887).
[268] Perkin, *J. Chem. Soc.,* **65,** 572 (1894).
[269] Haworth and Perkin, *J. Chem. Soc.,* **65,** 591 (1894).
[270] Errera and Perciabosco, *Ber.,* **33,** 2976 (1900).
[271] Engler and Meyer, *Ber.,* **38,** 2486 (1905).
[272] Thorpe and Young, *J. Chem. Soc.,* **77,** 937 (1900).
[273] Goldthwaite, *Am. Chem. J.,* **30,** 447 (1903).
[274] Noller and Adams, *J. Am. Chem. Soc.,* **48,** 2444 (1926).
[275] Benary and Schinkopf, *Ber.,* **56,** 354 (1923).
[276] V. Voorhees, Ph.D. Dissertation, University of Wisconsin, 1924.
[277] Heyl and Cope, *J. Am. Chem. Soc.,* **65,** 669 (1943).
[278] Dox and Thomas, *J. Am. Chem. Soc.,* **45,** 1811 (1923).

Likewise, for a given alkyl group the iodide is more reactive than the bromide,[34,37,40,142,234,279–281] which is more reactive than the chloride,[282–284] the fluoride being almost inert.[285] Since very reactive halogen compounds favor dialkylation (p. 121), it is usually advisable to select the least reactive halide as an alkylating agent where dialkylation is expected to be a serious side reaction.[140,280]

Alkyl halides that are readily dehydrohalogenated (e.g., tertiary alkyl halides) are unsuitable alkylating agents (p. 124), since the yield of alkylated product is materially reduced by the loss of both base and alkyl halide which accompanies dehydrohalogenation.[44,149,168,286] For example, one-third of the cyclohexyl bromide employed in the alkylation of diethyl malonate was converted to cyclohexene.[286]

Although the alkyl bromides are usually the most satisfactory alkylating agents, the alkyl chloride is recommended when the corresponding alkyl bromide is very reactive. If the alkyl bromide is relatively unreactive, use of the corresponding alkyl iodide is preferable. If the desired alkyl iodide is not available a satisfactory alternative employs mixtures of the alkyl bromide or alkyl chloride with sodium iodide[70,287–289,291] or potassium iodide[290,292] in alcoholic media.

Di- and Poly-halides. Alkylation reactions involving methylene chloride,[293,294] methylene bromide,[295] and methylene iodide[296–300] have been found to proceed normally. Such dihalides have been especially valuable for the preparation of cyclic systems.[296,299–302] However, a

[279] Rossolymo, *Ber.*, **22**, 1233 (1889).
[280] Bischoff, *Ber.*, **28**, 2616 (1895).
[281] Kuhn, Köhler, and Köhler, *Hoppe-Seyler's Z. physiol. Chem.*, **242**, 171 (1936).
[282] Rothstein, *Bull. soc. chim. France*, [5] **2**, 80 (1935).
[283] Noyes and Cox, *J. Am. Chem. Soc.*, **25**, 1093 (1903).
[284] Dey and Doraiswami, *J. Ind. Chem. Soc.*, **10**, 309 (1933).
[285] Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).
[286] Eykman, *Chem. Weekblad*, **6**, 699 (1909).
[287] Buu-Hoï and Cagniant, *Bull. soc. chim. France*, [5] **9**, 99 (1942).
[288] Gagnon, Savard, Gaudry, and Richardson, *Can. J. Research*, **25B**, 28 (1947).
[289] Birch and Robinson, *J. Chem. Soc.*, **1942**, 488.
[290] Rajzman, *Bull. soc. chim. France*, **1948**, 754.
[291] Buu-Hoï, Cagniant, and Janicaud, *Compt. rend.*, **212**, 1105 (1941).
[292] Pineau, *J. recherches centre natl. recherche sci.; Labs. Bellevue Paris*, **1951**, 292 [*C. A.*, **46**, 416 (1952)].
[293] Perkin and Prentice, *J. Chem. Soc.*, **59**, 990 (1891).
[294] Tutin, *J. Chem. Soc.*, **91**, 1141 (1907).
[295] Perkin and Scarborough, *J. Chem. Soc.*, **119**, 1400 (1921).
[296] Dressel and Guthzeit, *Ann.*, **256**, 171 (1890).
[297] Guthzeit and Dressel, *Ber.*, **21**, 2233 (1888).
[298] Zelinsky, *Ber.*, **22**, 3294 (1889).
[299] Perkin, *J. Chem. Soc.*, **59**, 798 (1891).
[300] Kötz and Stalmann, *J. prakt. Chem.*, [2] **68**, 156 (1903).
[301] Pospischill, *Ber.*, **31**, 1950 (1898).
[302] Thole and Thorpe, *J. Chem. Soc.*, **99**, 2183 (1911).

similar reaction involving benzylidene chloride and tetraethyl 1,1,5,5-pentanetetracarboxylate led to the formation of the doubly unsaturated

$$CH_2[CH(CO_2C_2H_5)_2]_2 + CH_2I_2 \xrightarrow{NaOC_2H_5}$$
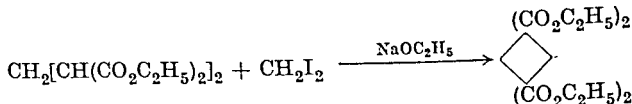
acid α,α'-dibenzylidenepimelic acid, after saponification and decarboxylation,[303] rather than a cyclic compound.

Chloroform, bromoform, iodoform, ethyl trichloroacetate, carbon tetrachloride, and carbon tetrabromide all react with diethyl sodiomalonate to form diethyl α,γ-dicarbethoxyglutaconate, although a similar reaction with 1,1,1-trichloroethane failed. Analogous products are formed with

$$CHCl_3 + 2CH_2(CO_2C_2H_5)_2 \xrightarrow[C_2H_5OH]{NaOC_2H_5} (C_2H_5O_2C)_2CHCH{=}C(CO_2C_2H_5)_2$$
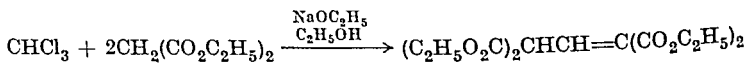
other active methylene compounds including ethyl cyanoacetate and malononitrile.[231] If monoalkylmalonic esters are utilized in a similar reaction, a mixture of products is formed in which either one or two of the halogen atoms of the haloform is retained.[231]

$$CH_3CH(CO_2C_2H_5)_2 + CHCl_3 \xrightarrow{Na, (C_2H_5)_2O} Cl_2CHC(CH_3)(CO_2C_2H_5)_2$$
$$+ (C_2H_5O_2C)_2C(CH_3)CHClC(CH_3)(CO_2C_2H_5)_2$$
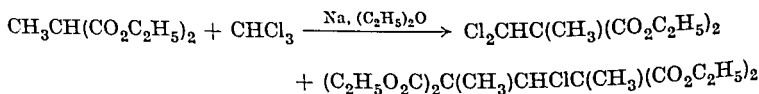
α,ω-Polymethylene dihalides have served as useful alkylating agents for the preparation of carbocyclic compounds with ring sizes ranging from three to seven.[92,170,269,304-310] A competing reaction results in the

$$Br(CH_2)_5Br + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5, C_2H_5OH}$$

$$+ (C_2H_5O_2C)_2CH(CH_2)_5CH(CO_2C_2H_5)_2$$
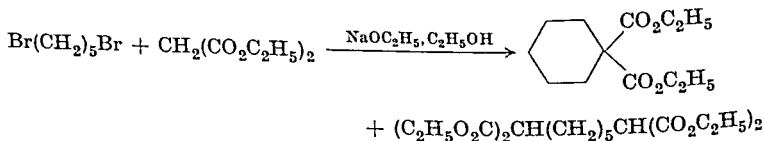
[303] Perkin and Prentice, J. Chem. Soc., **59**, 818 (1891).
[304] Dox and Yoder, J. Am. Chem. Soc., **43**, 1366 (1921).
[305] Knowles and Cloke, J. Am. Chem. Soc., **54**, 2028 (1932).
[306] Case, J. Am. Chem. Soc., **56**, 715 (1934).
[307] Weston, J. Am. Chem. Soc., **68**, 2345 (1946).
[308] Haworth and Perkin, J. Chem. Soc., **65**, 86 (1894).
[309] Carpenter and Perkin, J. Chem. Soc., **75**, 921 (1899).
[310] Best and Thorpe, J. Chem. Soc., **95**, 685 (1909).

simultaneous formation of the tetralkyl polymethylene-α,ω-dimalonate.[311] Although this tetracarboxylic ester is usually formed by attack of two diethyl malonate anions on the dihalide,[312] the cyclopropane derivative obtained when ethylene dibromide serves as the alkylating agent has been found to be susceptible to attack by the enolate of an active methylene compound.[310,312–314]   Thus the tetracarboxylic ester could be formed by either of two routes.   The yield of the cyclopropane is better if ethyl cyanoacetate is substituted for diethyl malonate.   As would be anticipated, the use of a large volume of solvent favors intramolecular alkylation leading to a cyclic product.[210,307]

$$BrCH_2CH_2Br + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \quad \rightarrow Br(CH_2)_2CH(CO_2C_2H_5)_2 + Br^{\ominus}$$

$$Br(CH_2)_2CH(CO_2C_2H_5)_2 \xrightarrow{\text{NaOC}_2\text{H}_5} \begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!\!>\!C(CO_2C_2H_5)_2$$

$$Br(CH_2)_2CH(CO_2C_2H_5)_2 + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow (C_2H_5O_2C)_2CH(CH_2)_2\overset{\displaystyle CO_2C_2H_5}{\underset{\displaystyle CO_2C_2H_5}{\overset{|}{\underset{|}{CH}}}}$$

$$\begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!\!>\!C(CO_2C_2H_5)_2 + CH_2(CO_2C_2H_5)_2 \xrightarrow{\text{NaOC}_2\text{H}_5}$$
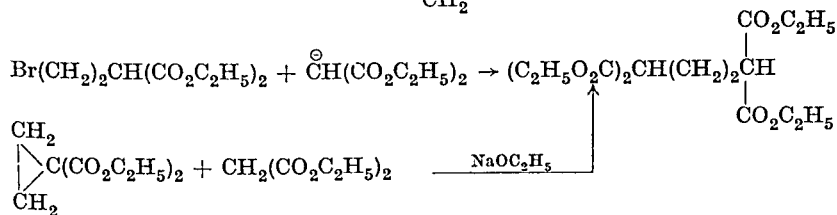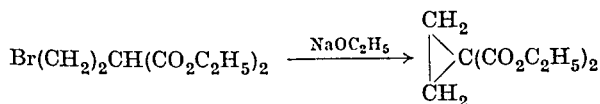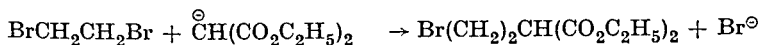
A similar synthesis of cyclopropane derivatives utilizes 1,4-dibromo-2-butene as the alkylating agent.[20]   The major products are tetraethyl 2-vinyl-1,1,4,4-butanetetracarboxylate and diethyl 2-vinyl-1,1-cyclopropanedicarboxylate, the cyclopropane derivative apparently having been formed by an intramolecular S_N2' process (p. 112).

$$BrCH_2CH\!\!=\!\!CHCH_2Br + CH_2(CO_2C_2H_5)_2 \xrightarrow[\text{C}_2\text{H}_5\text{OH}]{\text{NaOC}_2\text{H}_5}$$

$$CH_2\!\!=\!\!CH\!\!-\!\!\underset{\underset{\displaystyle CH_2}{\diagdown\diagup}}{CH}\!\!-\!\!C(CO_2C_2H_5)_2 + CH_2\!\!=\!\!CH\!\!-\!\!\underset{\displaystyle CH_2CH(CO_2C_2H_5)_2}{\overset{|}{CHCH(CO_2C_2H_5)_2}}$$

$$+ (C_2H_5O_2C)_2CHCH_2CH\!\!=\!\!CHCH_2CH(CO_2C_2H_5)_2$$
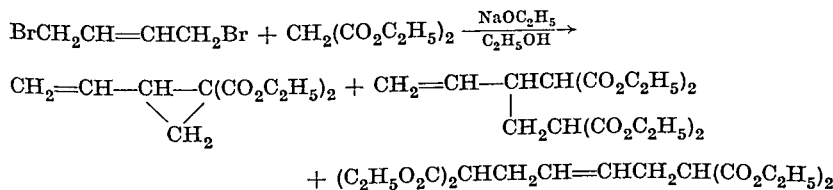
It has proved difficult to arrest the reaction of polymethylene dihalides and sodiomalonic ester at the monoalkylation stage, since the intramolecular and intermolecular dialkylation reactions described previously

[311] Freer and Perkin, *J. Chem. Soc.*, **53**, 215 (1888).
[312] Bone and Perkin, *J. Chem. Soc.*, **67**, 108 (1895).
[313] Mitchell and Thorpe, *J. Chem. Soc.*, **97**, 997 (1910).
[311] Kierstead, Linstead, and Weedon, *J. Chem. Soc.*, **1952**, 3616.

often predominate.   However, diethyl γ-bromopropylmalonate has been prepared in 70% yield by the use of a large excess of 1,3-dibromopropane with diethyl malonate.[131]   An alternative synthesis for such compounds involves the initial formation of a terminal methylene derivative of malonic ester followed by the peroxide-catalyzed addition of hydrogen bromide.[210,315]

$$CH_2=CHCH_2Br + \overset{\ominus}{C}H(CO_2C_2H_5)_2 \rightarrow CH_2=CHCH_2CH(CO_2C_2H_5)_2 + \overset{\ominus}{B}r$$

$$CH_2=CHCH_2CH(CO_2C_2H_5)_2 + HBr \xrightarrow[\text{catalyst}]{\text{Peroxide}} Br(CH_2)_3CH(CO_2C_2H_5)_2$$
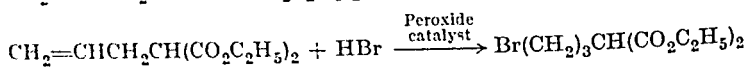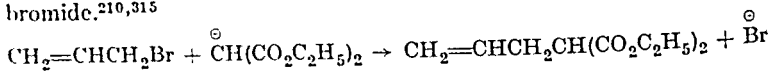
Monoalkylation of diethyl sodiomalonate with 1-chloro-3-iodopropane would be expected to produce diethyl γ-chloropropylmalonate, displacement having involved the more reactive carbon-iodine bond.   However, the alcohol-soluble sodium iodide produced in the reaction mixture converted the chloro ester in part to the corresponding iodo compound. When excess sodium iodide was added to the reaction mixture, only diethyl γ-iodopropylmalonate could be isolated.[92]   In the preparation of diethyl (β-chloroethyl)isoamylmalonate from 1-chloro-2-iodoethane and diethyl isoamylmalonate this problem was avoided by the use of a benzene solution in which sodium iodide is insoluble.[316]

Where one of the halogens of the dihalide is bonded to a secondary carbon atom, some dehydrohalogenation may be expected to accompany alkylation.[160]   Halogen atoms bonded to tertiary carbon atoms are lost as the corresponding hydrogen halide.[173,317,318]

As described earlier (p. 125) certain vicinal dihalides, especially those compounds in which the halogen atoms are bonded to secondary and tertiary carbon atoms, tend to lose the halogen with the resulting formation of an olefin and the coupled product from two molecules of the active methylene compound.   Other vicinal dihalides such as 1,2-dichlorocyclohexane,[150] 1,2-dibromocyclohexane,[150,286,319] 1,2-dibromotetrahydronaphthalene,[150,320] and 2,3-dibromodecahydronaphthalene[150] undergo
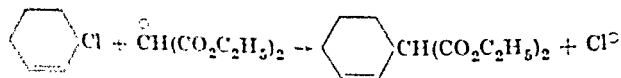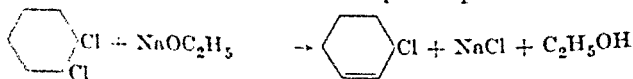
both alkylation and dehydrohalogenation reactions. Thus the product formed from the 1,2-dihalocyclohexanes was the same as the product formed from 2-cyclohexenyl chloride[150] or 2-cyclohexenyl bromide.[319] Since the alkylation of 1,2-dichlorocyclohexane with diethyl sodiomalonate proceeds much more rapidly than the analogous reaction with cyclohexyl chloride,[150] dehydrochlorination is presumed to be the first step in the reaction sequence. With 2,3-dibromotetrahydronaphthalene only dehydrohalogenation occurred, the product being naphthalene.[320]

The reaction of 1,2-dithiocyanocyclohexane with diethyl malonate is completely analogous to the reaction of the 1,2-dihalocyclohexanes. One thiocyano group is lost in an elimination reaction, and the other group is displaced with the production of diethyl 2-cyclohexenylmalonate.[322]

Vinyl and Aryl Halides. Although vinyl and aryl halides, being inert to nucleophilic displacement reactions, are generally of no value as alkylating agents, several successful alkylation reactions involving such halides have been reported. Thus 1,2-dibromoethylene reacted with diethyl ethylmalonate to yield diethyl ethyl-(β-bromovinyl)malonate.[54] However, 1,2-dichloroethylene failed to alkylate malonic ester.[275] The successful alkylation of acetonitrile with chlorobenzene in the presence of potassium amide and liquid ammonia[323] may be likened to the conversion of chlorobenzene to aniline under similar conditions,[324] in which the amino group may become attached either to the carbon atom from which the chlorine atom is displaced or to an adjacent carbon atom. It is not known whether the position at which the cyanomethyl group enters and the position occupied by the leaving chlorine atom are the same.

If the carbon-halogen bond of the aryl halide is activated by the introduction of electron-attracting groups *ortho* and *para* to the halogen atom, then successful arylation will occur. For example, ethyl *p*-nitrophenylcyanoacetate has been prepared from *p*-nitrochlorobenzene and ethyl cyanoacetate.[325] However, it will be recalled that such electron-attracting substituents also promote decarbethoxylation (p. 127). When diethyl 2,4-dinitrophenylmalonate was treated with 2,4-dinitrobromobenzene in ethanolic sodium ethoxide, only ethyl *bis*-(2,4-dinitrophenyl)acetate could be isolated.[184] Replacement of halogen atoms situated on negatively substituted benzene rings by hydrogen has also been observed during alkylation reactions.[326–328]

[321] Cagniant and Buu-Hoï, *Bull. soc. chim. France*, [5] 9, 111 (1942).
[322] Mousseron and Winternitz, *Bull. soc. chim. France*, [5] 11, 120 (1944).
[323] Bergstrom and Agostinho, *J. Am. Chem. Soc.*, 67, 2152 (1945).
[324] Roberts, Simmons, Carlsmith, and Vaughan, *J. Am. Chem. Soc.*, 75, 3290 (1953).
[325] Fairbourne and Fawson, *J. Chem. Soc.*, 1927, 46.
[326] Jackson and Robinson, *Am. Chem. J.*, 11, 93 (1889).
[327] Jackson and Robinson, *Am. Chem. J.*, 11, 541 (1889).
[328] Jackson and Robinson, *Ber.*, 21, 2034 (1888).

The 2- and 4-halopyridines and the 2- and 4-chloroquinolines, whose reactivity may be likened to that of the nitrochlorobenzenes just described, also serve as effective alkylating agents.

Epoxides. Epoxides have served as alkylating agents for malonic esters, cyanoacetic esters, monocarboxylic esters, and mononitriles. Except in sterically unfavorable instances,[7] the intermediate hydroxy esters or hydroxy nitriles are converted to the corresponding lactones or cyclic imido esters.[27,329] The same products are formed if the corresponding alkene halohydrins are utilized.

Dialkyl Carbonates. The dialkyl carbonates cannot be used to alkylate malonic ester,[330] monocarboxylic esters,[43,129,331,332] or mononitriles[185,186,189,333] because carbethoxylation of the intermediate anion (p. 128) takes precedence over alkylation. With primary alkylmalonic esters the dialkyl carbonates may be used as alkylating agents, the dialkylated product being obtained in yields of 25–80%.[330] The dialkyl carbonates are unsatisfactory alkylating agents for secondary alkylmalonic esters and for alkylcyanoacetic esters.[330]

Dialkyl Sulfates, Alkyl Sulfonates, and Nitrates. Both dimethyl sulfate and diethyl sulfate have been used extensively for the alkylation of all types of active methylene compounds. The yields obtained with these alkylating agents and with the corresponding alkyl iodides are usually similar. In addition the high boiling points of the dialkyl sulfates permit the use of higher reaction temperatures without loss of the alkylating agent.[249]

The alkyl benzenesulfonates and the alkyl *p*-toluenesulfonates have been used to advantage as alkylating agents.[69] As in the case of the alkyl halides the yields of alkylated products derived from primary alkyl sulfonates are good, but only fair yields are obtained with the sulfonate esters of secondary alcohols. In addition to their high boiling points, the alkyl sulfonates are valuable alkylating agents where conversion of the corresponding alcohol to the alkyl halide is difficult or involves rearrangement.[238,334,335]

Benzyl nitrate has served as an alkylating agent for malonic ester, both mono- and di-alkylation products being obtained.[336]

[329] Easton, Gardner, and Stevens, *J. Am. Chem. Soc.*, **69**, 2941 (1947).

[330] Wallingford and Jones, *J. Am. Chem. Soc.*, **64**, 578 (1942).

[331] Nelson and Cretcher, *J. Am. Chem. Soc.*, **50**, 2758 (1928).

[332] Hauser, Abramovitch, and Adams, *J. Am. Chem. Soc.*, **64**, 2714 (1942).

[333] Hessler, *Am. Chem. J.*, **32**, 119 (1904).

[334] Braker, Pribyl, and Lott, *J. Am. Chem. Soc.*, **69**, 866 (1947).

[335] Peacock and Tha, *J. Chem. Soc.*, **1928**, 2303.

[336] Nef, *Ann.*, **309**, 171 (1899).

component in an acetic acid-piperidine mixture is hydrogenated over palladium on charcoal. This process, termed reductive alkylation, has been found to produce certain alkylcyanoacetic esters in yields of 39–98%.[362–364]

Reductions of alkylidene derivatives and reductive alkylation are advantageous in that dialkylation, a side reaction in alkylation procedures, is avoided.[363] The use of platinum oxide as the catalyst for reductive alkylation may result in partial reduction of the nitrile group in addition to the expected reductive alkylation.[363]

Addition of Grignard Reagents to Alkylidene Derivatives (Tables XVIII and XIX). Extensive dehydrohalogenation precludes the use of tertiary alkyl halides for the preparation of tertiary alkyl derivatives of active methylene compounds (pp. 112, 124, 139). Such tertiary alkyl derivatives can be prepared by the addition of Grignard reagents to the alkylidene derivatives obtained by the condensation of malonic or cyanoacetic esters with a ketone. The mode of addition of Grignard reagents to

$$(CH_3)_2C = C(CO_2C_2H_5)_2 + CH_3MgI \rightarrow (CH_3)_3CCH(CO_2C_2H_5)_2$$
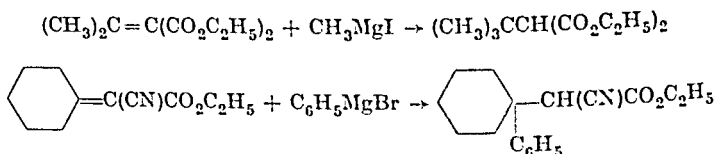
substituted cinnamonitriles is dependent on the structure of the unsaturated compound. Normally, 1,2 addition occurs forming an imino compound;[365,366] however, if a large group is bonded to the α-carbon atom, 1,4 addition leading to a saturated nitrile has been observed.[365,366] The addition of aliphatic Grignard reagents to alkylidene derivatives is often accompanied by reduction of the double bond in the alkylidene compound as a side reaction.[367] The substitution of the appropriate dialkyl- or diarylcadmium for the Grignard reagent has resulted in the formation of the alkylated product in poor yield.[367] The addition of copper salts to the reaction mixture has been reported to favor the 1,4-addition of Grignard reagents to alkylidenemalonic esters.[368]

Condensation of Aromatic Compounds with Mesoxalic and Tartronic Esters (Table XX). Direct alkylation methods usually cannot be applied to the preparation of aryl- and diaryl-malonic esters (p. 143).

[363] Alexander and Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).
[364] Sharp and Dohme, Brit. pat. 606,962 [*C. A.*, **43**, 1436 (1949)].
[365] Kohler, *Am. Chem. J.*, **35**, 386 (1906).
[366] Henze and Swett, *J. Am. Chem. Soc.*, **73**, 4918 (1951).
[367] Prout, Huang, Hartman, and Korpics, *J. Am. Chem. Soc.*, **76**, 1911 (1954).
[368] Brandström and Forsblad, *Arkiv Kemi*, **6**, 561 (1954).

Aryl-substituted malonic esters have been obtained from diethyl mesoxalate, an oxidation product of diethyl malonate.[369] The aryltartronic esters have been obtained either by the condensation of mesoxalic ester with aromatic hydrocarbons in the presence of sulfuric acid or stannic chloride[370,371] or by the addition of Grignard reagents to mesoxalic ester

$$OC(CO_2C_2H_5)_2 + \underset{CH_3}{\overset{CH_3}{\bigcirc}} \xrightarrow{SnCl_4} \underset{CH_3}{\overset{CH_3}{\bigcirc}}\overset{OH}{\underset{|}{-C(CO_2C_2H_5)_2}}$$
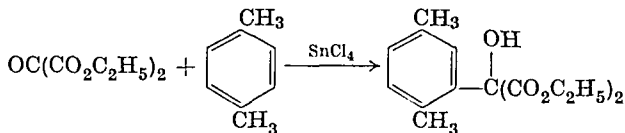
at -70%.[372] Diethyl 9-phenanthryltartronate has been converted to 9-phenanthrylmalonic ester by the replacement of the hydroxyl group by a chlorine atom followed by reduction.[372]

The diarylmalonic esters have been prepared by the condensation of aromatic hydrocarbons with either mesoxalic esters or aryltartronic esters in the presence of sulfuric acid or phosphorus oxychloride.[373]

$$p\text{-}(CH_3)_2NC_6H_4\overset{OH}{\underset{|}{C}}(CO_2C_2H_5)_2 + (CH_3)_2NC_6H_5 \xrightarrow{POCl_3}$$

$$[p\text{-}(CH_3)_2NC_6H_4]_2C(CO_2C_2H_5)_2$$
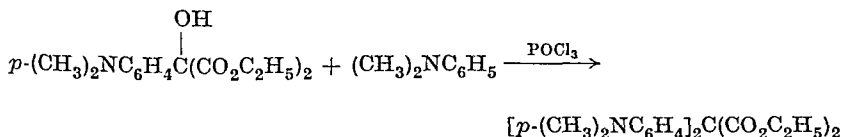
Other Methods. Among other methods available for the preparation of alkyl- or aryl-malonic esters is the condensation of diethyl oxalate with the appropriately substituted acetic ester.[179] The resultant ethoxalyl derivative is then decarbonylated thermally with [374] or without[375-378] powdered soft glass. This method is of value not only for the preparation

$$C_6H_5CH_2CO_2C_2H_5 + (CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} C_6H_5CH(CO_2C_2H_5)COCO_2C_2H_5$$

$$C_6H_5CH(CO_2C_2H_5)COCO_2C_2H_5 \rightarrow CO + C_6H_5CH(CO_2C_2H_5)_2$$
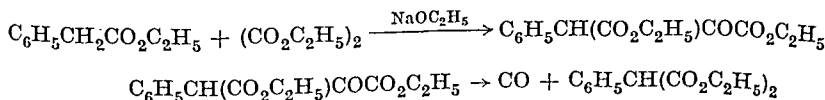
[369] Dox, *Org. Syntheses, Coll. Vol.* 1, John Wiley & Sons, New York, 1941, p. 266.

[370] Riebsomer and Irvine, *Org. Syntheses*, 25, 33 (1945).

[371] Riebsomer, Wiseman, and Condike, *Proc. Indiana Acad. Sci.*, 50, 80 (1940) [*C. A.*, 35, 5476 (1941)].

[372] Cope and Field, *J. Org. Chem.*, 14, 856 (1949).

[373] Guyot and Michel, *Compt. rend.*, 148, 229 (1909).

[374] Blicke and Zienty, *J. Am. Chem. Soc.*, 63, 2779 (1941).

[375] Rising and Stieglitz, *J. Am. Chem. Soc.*, 40, 723 (1918).

[376] Keach, *J. Am. Chem. Soc.*, 55, 3440 (1933).

[377] Lauer and Hansen, *J. Am. Chem. Soc.*, 61, 3039 (1939).

[378] Levene and Meyer, *Org. Syntheses, Coll. Vol.* 2, John Wiley & Sons, New York, 1943, p. 288.

of arylmalonic esters unobtainable by direct alkylation,[379] but also for the preparation of low-molecular-weight monoalkylmalonic esters whose separation from the malonic ester and dialkylmalonic ester present in the product obtained by direct alkylation is difficult (p. 123).[69,380,381]

A more direct method of carbethoxylation involves the use of diethyl carbonate in the presence of sodium ethoxide. This method is applicable to the synthesis of alkyl and aryl derivatives of malonic ester[43,129,330–332] and cyanoacetic ester,[185–189,331,333] the best yields being obtained in the case of the aryl derivatives. Dialkylacetic esters cannot be carbethoxylated by this method.[43]

The alkylation of aromatic hydrocarbons with α-bromoarylacetic esters, α-bromoarylacetonitriles, or α-bromodiarylacetonitriles in a Friedel-Crafts reaction has served to produce diarylacetic esters,[382] diarylacetonitriles,[27,382,383] and triarylacetonitriles.[383]

Diethyl cyclopropylmalonate has been prepared from cyclopropanecarboxylic acid by means of the reaction sequence illustrated with the accompanying equations.[384]

$$\begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!>\!CHCOBr + N_2CHCO_2C_2H_5 \quad \rightarrow \quad \begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!>\!CHCOCN_2CO_2C_2H_5$$

$$\begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!>\!CHCOCN_2CO_2C_2H_5 \quad \xrightarrow{\text{Ag}_2O} \quad \begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!>\!CHC\!\!=\!\!C\!\!=\!\!O \atop CO_2C_2H_5$$

$$\begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!>\!CHC\!\!=\!\!C\!\!=\!\!O \atop CO_2C_2H_5 + C_2H_5OH \quad \rightarrow \quad \begin{array}{c} CH_2 \\ | \\ CH_2 \end{array}\!\!>\!CHCH(CO_2C_2H_5)_2$$
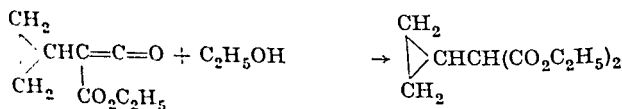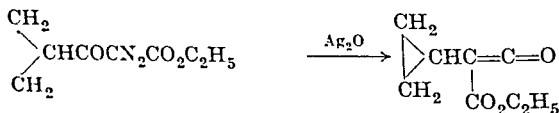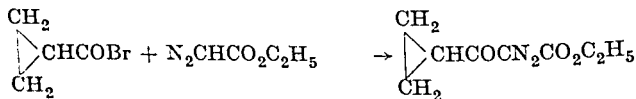
The alkylation of cyanoketene dimethyl acetal with benzyl bromide gave, after acidification, methyl benzylcyanoacetate (21%) and methyl dibenzylcyanoacetate (26%).[385]

SYNTHETIC APPLICATIONS OF THE ALKYLATION REACTION

The alkylation of active methylene compounds affords a convenient synthetic route to mono-, di-, and tri-substituted derivatives of acetic acid and acetonitrile in which the carbon chain of the alkylating agent has been lengthened by two atoms. Substituted acetic acids are often prepared from the corresponding malonic esters by saponification with aqueous alkali (p. 157) followed by decarboxylation of the substituted malonic acid. With ethyl esters the course of the saponification step may be followed by distilling the ethanol from the reaction mixture as it is formed. With low-molecular-weight substituted malonic acids, decarboxylation is most easily effected by boiling a solution of the malonic acid in 20% (constant-boiling) aqueous hydrochloric acid or aqueous sulfuric acid. The saponification and decarboxylation may be done in the same reaction vessel if a calculated excess of concentrated hydrochloric or sulfuric acid is added to the reaction mixture obtained from the saponification.[14,386] It is usually more satisfactory to isolate substituted malonic acids of high molecular weight. These acids lose carbon dioxide when they are heated above their melting points.[387] Alternatively, a solution of the substituted malonic acid in a high-boiling solvent such as xylene may be boiled under reflux until decarboxylation is complete.

$$\underset{R'}{\overset{R}{>}}C(CO_2C_2H_5)_2 \rightarrow \underset{R'}{\overset{R}{>}}C(CO_2{}^{\ominus}Na^{\oplus})_2 \rightarrow \underset{R'}{\overset{R}{>}}C(CO_2H)_2 \rightarrow \underset{R'}{\overset{R}{>}}CHCO_2H + CO_2$$
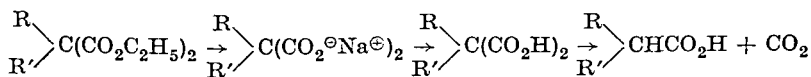
The saponification of substituted cyanoacetic esters followed by the thermal decarboxylation of the corresponding cyanoacetic acid yields substituted acetonitriles.

$$\underset{R'}{\overset{R}{>}}C(CN)CO_2C_2H_5 \rightarrow \underset{R'}{\overset{R}{>}}C(CN)CO_2{}^{\ominus}Na^{\ominus} \rightarrow \underset{R'}{\overset{R}{>}}C(CN)CO_2H \rightarrow \underset{R'}{\overset{R}{>}}CHCN + CO_2$$
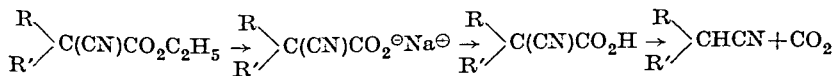
Substituted malonic and cyanoacetic esters may be hydrolyzed and decarboxylated to yield substituted acetic acids in one step by treatment with boiling aqueous acids.[388]

[386] Reid and Ruhoff, *Org. Syntheses, Coll. Vol. 2,* John Wiley & Sons, New York, 1943, p. 474.

[387] Marvel and du Vigneaud, *Org. Syntheses, Coll. Vol. 2,* John Wiley & Sons, New York, 1943, p. 94.

[388] Clarke and Murray, *Org. Syntheses, Coll. Vol. 1,* John Wiley & Sons, New York, 1941, p. 523.

t-Butyl,[389] tetrahydropyranyl,[390] and benzhydryl[224] esters of substituted malonic acids undergo fission of the carbon-oxygen bond of the ester in acidic media.   This rapid fission of *t*-butyl esters[392] and tetrahydropyranyl esters[390] has been utilized for the synthesis of easily reducible ketones,[390,393]

$$p\text{-}O_2NC_6H_4COC(CH_2C_6H_5)(CO_2C_4H_9\text{-}t)_2 \xrightarrow{\;H^{\oplus}\;} p\text{-}O_2NC_6H_4COCH_2CH_2C_6H_5$$
$$+\ 2CO_2 + 2(CH_3)_2C{=}CH_2$$
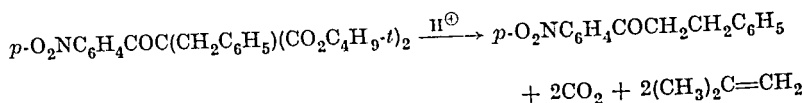
by the acidic hydrolysis and decarboxylation of acylmalonic esters.   The use of benzyl esters[394-396] which can be cleaved by hydrogenolysis[397] is not feasible for the synthesis of compounds with easily reducible groups. The use of the acid-labile *t*-butyl and tetrahydropyranyl esters is to be recommended for the preparation of substituted malonic or cyanoacetic acids containing other functions which would not survive the reaction conditions required for the hydrolysis of the ethyl esters.   The reversible nature of the acidic cleavage permits the synthesis of *t*-butyl esters by the condensation of carboxylic acids and isobutylene in an acidic medium;[393] tetrahydropyranyl esters may be prepared similarly from dihydropyran.

$$CH_2(CO_2H)_2 + 2(CH_3)_2C{=}CH_2 + 2H^{\oplus} \rightleftarrows CH_2(CO_2C_4H_9\text{-}t)_2$$
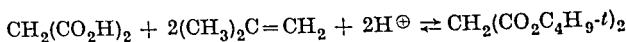
An alternative method for the conversion of diethyl dialkylmalonates to ethyl dialkylacetates involves the removal of a carbethoxyl group at high temperatures.   This change is most easily effected by heating an ethanolic solution of the diethyl dialkylmalonate to 250° in the presence of sodium ethoxide (p. 127).   Under such conditions diethyl diethyl-malonate was converted to ethyl diethylacetate in 82% yield.[180]   When an ethereal solution of diethyl diethylmalonate was heated with 2 gram atoms of sodium metal, carbon monoxide (85%) was evolved and ethyl

[389] Cohen and Schneider, *J. Am. Chem. Soc.*, **63**, 3382 (1941).

[390] Bowman and Fordham, *J. Chem. Soc.*, **1952**, 3945.

[391] Strain, Plati, and Warren, *J. Am. Chem. Soc.*, **64**, 1436 (1942).

[392] Breslow, Baumgarten, and Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).

[393] Fonken and Johnson, *J. Am. Chem. Soc.*, **74**, 831 (1952).

[394] Bowman, *J. Chem. Soc.*, **1950**, 325.

[395] Ames and Bowman, *J. Chem. Soc.*, **1951**, 1079.

[396] Bowman and Fordham, *J. Chem. Soc.*, **1951**, 2758.

[397] Hartung and Simonoff in Adams, *Organic Reactions*, Vol. 7, Chapter 5, John Wiley & Sons, New York, 1953, pp. 263–326.

diethylacetate was formed in 46% yield.[398] Similarly, diethyl diethyl-malonate, when heated with ethanol-free sodium ethoxide to 220–230°, yielded ethyl diethylacetate (67%), ether (8%), diethyl carbonate (16%), ethylene (14%), carbon monoxide (25%), and ethanol.[180] The diethyl carbonate was presumably formed from the ethanol generated in the reaction mixture (p. 127).

Substituted acetic acids prepared by means of the alkylation reaction have been used to prepare long-chain hydrocarbons of known structure,[46,141,399,400] hydrindones,[114,401–410] tetralones,[321,411–423] and hydrotetralones.[424–426]

A number of amino acid syntheses have utilized such starting materials as chloromalonic ester,[209] alkylmalonic esters,[118,119,132,427–433] aminomalonic

[398] Krollpfeiffer and Rosenberg, *Ber.*, **69**, 465 (1936).

[399] Levene and Taylor, *J. Biol. Chem.*, **54**, 351 (1922).

[400] Grimshaw, Guy, and Smith, *J. Chem. Soc.*, **1940**, 68.

[401] Lecocq, *Ann. chim. Paris*, [12] **3**, 62 (1948).

[402] von Braun and Friedsam, *Ber.*, **65**, 1680 (1932).

[403] Cagniant and Buu-Hoï, *Bull. soc. chim. France*, [5] **9**, 119 (1942).

[404] Cagniant, *Bull. soc. chim. France*, [5] **9**, 884 (1942).

[405] Buu-Hoï and Cagniant, *Bull. soc. chim. France*, [5] **10**, 151 (1943).

[406] Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 2174 (1935).

[407] Bruce and Kahn, *J. Am. Chem. Soc.*, **60**, 1017 (1938).

[408] Bruce and Todd, *J. Am. Chem. Soc.*, **61**, 157 (1939).

[409] Fieser and Gates, *J. Am. Chem. Soc.*, **62**, 2335 (1940).

[410] Martin, *J. Chem. Soc.*, **1941**, 679.

[411] Lévy, *Ann. chim. Paris*, [11] **9**, 44 (1938).

[412] Buchta, Galster, and Luther, *Chem. Ber.*, **82**, 126 (1949).

[413] Cagniant and Buu-Hoï, *Bull. soc. chim. France*, [5] **9**, 841 (1942).

[414] Buu-Hoï and Cagniant, *Compt. rend.*, **214**, 115 (1942).

[415] Ruzicka and Mingazzini, *Helv. Chim. Acta*, **5**, 710 (1922).

[416] Ruzicka and Ehmann, *Helv. Chim. Acta*, **15**, 140 (1932).

[417] Ruzicka, Ehmann, and Mörgeli, *Helv. Chim. Acta*, **16**, 314 (1933).

[418] Rapson and Short, *J. Chem. Soc.*, **1933**, 128.

[419] Kon, Narracott, and Reid, *J. Chem. Soc.*, **1938**, 778.

[420] Cocker and Hayes, *J. Chem. Soc.*, **1951**, 844.

[421] Chakravarti, *J. Indian Chem. Soc.*, **20**, 393 (1943).

[422] Dhekne and Bhide, *J. Indian Chem. Soc.*, **28**, 504 (1951).

[423] Späth and Hromatka, *Monatsh. Chem.*, **60**, 117 (1932).

[424] Chuang, Tien, and Ma, *Ber.*, **69**, 1494 (1936).

[425] Cook and Lawrence, *J. Chem. Soc.*, **1935**, 1637.

[426] Cook and Lawrence, *J. Chem. Soc.*, **1937**, 817.

[427] Fischer and Schmitz, *Ber.*, **39**, 351 (1906).

[428] Fischer and Schmitz, *Ber.*, **39**, 2209 (1906).

[429] von Braun and Kruber, *Ber.*, **45**, 384 (1912).

[430] Curtius and Sieber, *Ber.*, **55**, 1543 (1922).

[431] Sayles and Degering, *J. Am. Chem. Soc.*, **71**, 3161 (1949).

[432] Carter, *J. Biol. Chem.*, **108**, 619 (1935).

[433] Barry and Hartung, *J. Org. Chem.*, **12**, 460 (1947).

esters,[434, 435] formamidomalonic ester,[246, 436, 437] acetamidomalonic ester,[49,232,234,235,438–452,454–457] benzamidomalonic ester,[233,453,458,459] phthalimidomalonic ester,[236,460–468] alkylcyanoacetic esters,[127,128,185,288,469–472] and acylaminocyanoacetic esters.[241,242,448]

The reaction sequence utilized for the preparation of amino acids from aminomalonic esters, acylaminomalonic esters, or acylaminocyanoacetic esters involves alkylation followed by saponification and decarboxylation. Finally the acyl group is removed by acid hydrolysis. By the appropriate

$$RCONHCH(CO_2C_2H_5)_2 \rightarrow RCONHC(R')(CO_2C_2H_5)_2$$
$$\rightarrow RCONHC(R')CO_2H \rightarrow R'CH(NH_2)CO_2H$$
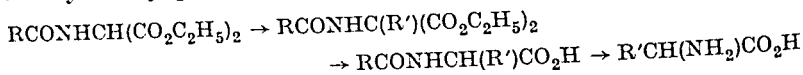
[434] Putochin, *Ber.*, **56**, 2213 (1923).

[435] Locquin and Cerchez, *Bull. soc. chim. France*, [4] **47**, 1386 (1930).

[436] Capková-Jirků, Koštíř, and Vondráček, *Chem. Listy*, **44**, 19 (1950) [*C. A.*, **45**, 8004 (1951)].

[437] Weisiger, *J. Biol. Chem.*, **186**, 591 (1950).

[438] Harington, *Biochem. J.*, **43**, 434 (1948).

[439] Šorm and Procházka, *Chem. Listy*, **46**, 490 (1952) [*C. A.*, **47**, 3798 (1953)].

[440] Erlenmeyer and Grubenmann, *Helv. Chim. Acta*, **30**, 297 (1947).

[441] Snyder and Pilgrim, *J. Am. Chem. Soc.*, **70**, 1962 (1948).

[442] Goering, Cristol, and Dittmer, *J. Am. Chem. Soc.*, **70**, 3310 (1948).

[443] Jones and McLaughlin, *J. Am. Chem. Soc.*, **71**, 2444 (1949).

[444] Bennett and Niemann, *J. Am. Chem. Soc.*, **72**, 1800 (1950).

[445] Bennett and Niemann, *J. Am. Chem. Soc.*, **72**, 1806 (1950).

[446] Jones, Kornfeld, and McLaughlin, *J. Am. Chem. Soc.*, **72**, 4526 (1950).

[447] Degering and Boatright, *J. Am. Chem. Soc.*, **72**, 5137 (1950).

[448] Burckhalter and Stephens, *J. Am. Chem. Soc.*, **73**, 56 (1951).

[449] Albertson, *J. Am. Chem. Soc.*, **73**, 452 (1951).

[450] Caldwell and Fox, *J. Am. Chem. Soc.*, **73**, 2935 (1951).

[451] Burckhalter and Stephens *J. Am. Chem. Soc.* **73**, 3502 (1951).

[452] Herz, Dittmer, and Cristol, *J. Biol. Chem.*, **171**, 383 (1947).

[453] Evans and Walker, *J. Chem. Soc.*, **1947**, 1571.

[454] Elliott and Harington, *J. Chem. Soc.*, **1949**, 1374.

[455] Mamalis, Petrow, and Sturgeon, *J. Chem. Soc.*, **1950**, 1600.

[456] Dalglicsh, *J. Chem. Soc.*, **1952**, 137.

[457] Armstrong and Lewis, *J. Org. Chem.*, **17**, 618 (1952).

[458] Niemann, Lewis, and Hays, *J. Am. Chem. Soc.*, **64**, 1678 (1942).

[459] Dunn, Smart, Redemann, and Brown, *J. Biol. Chem.*, **94**, 599 (1931–1932).

[460] Kuhn and Quadbeck, *Ber.*, **76**, 527 (1943).

[461] Kuhn and Quadbeck, *Ber.*, **76**, 529 (1943).

[462] Sörensen, *Bull. soc. chim. France*, [3] **33**, 1042 (1905).

[463] Sörensen, *Bull. soc. chim. France*, [3] **33**, 1052 (1905).

[464] Dey, *J. Chem. Soc.*, **1937**, 1166.

[465] Booth, Burnop, and Jones, *J. Chem. Soc.*, **1944**, 666.

[466] Barger and Weichselbaum, *Org. Syntheses*, Coll. Vol. 2, John Wiley & Sons, New York, 1943, p. 384.

[467] Dunn and Smart, *Org. Syntheses*, **30**, 7 (1950).

[468] Overhoff, Boeke, and Gorter, *Rec. trav. chim.*, **55**, 293 (1936).

[469] Gagnon and Nolin, *Can. J. Research*, **27B**, 742 (1949).

[470] Gagnon, Boivin, and Craig, *Can. J. Chemistry*, **29**, 70 (1951).

[471] Boivin, Gagnon, Renaud, and Bridgeo, *Can. J. Chemistry*, **30**, 994 (1952).

[472] Curtius and Benckiser, *J. prakt. Chem.*, [2] **125**, 236 (1930).

$$\text{RCH(CO}_2\text{K)CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{N}_2\text{H}_4} \text{RCH(CO}_2\text{K)CONHNH}_2 \xrightarrow{\text{HNO}_2}$$

$$\text{RCH(CO}_2\text{K)CON}_3 \rightarrow \text{RCH} \overset{\text{CO---O}}{\underset{\text{NH---CO}}{\diagup\diagdown}} \rightarrow \text{RCH(NH}_2\text{)CO}_2\text{H}$$

$$\text{RCH(CN)CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{N}_2\text{H}_4} \text{RCH(CN)CONHNH}_2 \xrightarrow{\text{HNO}_2} \text{RCH(CN)CON}_3$$

$$\rightarrow \text{RCH(NH}_2\text{)CN} \rightarrow \text{RCH(NH}_2\text{)CO}_2\text{H}$$
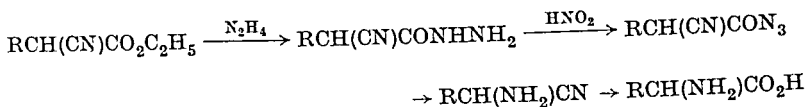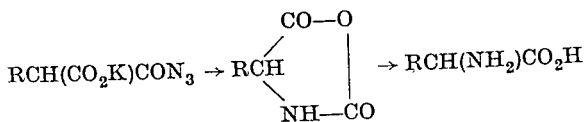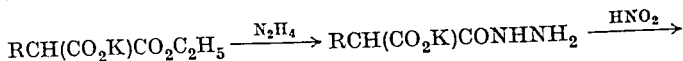
and some large-ring compounds[219,269,306,492,493] are readily accessible with the use of dihalogenated alkylating agents or ω-haloalkyl derivatives of active methylene compounds. Alkylating agents of the type $\text{Z(CH}_2\text{CH}_2\text{Cl)}_2$, where Z is an oxygen, sulfur, or nitrogen atom, have been used to synthesize tetrahydropyrans,[77,494,496–499] tetrahydrothiopyrans,[77,499] and piperidines.[77,495,501,503–505] The synthesis of certain polynuclear hydrocarbons by the method of Darzens[506–516] and by related

[492] Kenner, *J. Chem. Soc.*, **103**, 613 (1913).

[493] Franke and Hankam, *Monatsh. Chem.*, **31**, 177 (1910).

[494] von Braun and Köhler, *Ber.*, **50**, 1657 (1917).

[495] Büchi, Leuenberger, and Lieberherr, *Farm. sci. e tec. Pavia*, **6**, 429 (1951) [*C. A.*, **46**, 8015 (1952)].

[496] Kamm and Waldo, *J. Am. Chem. Soc.* **43**, 2223 (1921).

[497] Henze and McKee, *J. Am. Chem. Soc.*, **64**, 1672 (1942).

[498] Gibson and Johnson, *J. Chem. Soc.*, **1930**, 2525.

[499] Eisleb, U.S. pat. 2,242,575 [*C. A.*, **35**, 5647 (1941)].

[500] Bergel, Morrison, and Rinderknecht *J. Chem. Soc.*, **1944**, 267.

[501] Morrison and Rinderknecht *J. Chem. Soc.* **1950**, 1467.

[502] Avison and Morrison *J. Chem. Soc.* **1950**, 1471.

[503] Eisleb, Brit. pat. 501,135 [*C. A.*, **33**, 5872 (1939)].

[504] Tanabe Drug Co., Jap. pat. 153,615 [*C. A.*, **43**, 3471 (1949)].

[505] Eisleb, U.S. pat. 2,167,351 [*C. A.*, **33**, 8923 (1939)].

[506] Darzens, *Compt. rend.*, **183**, 748 (1926).

[507] Darzens and Heinz, *Compt. rend.*, **184**, 33 (1927).

[508] Darzens, *Compt. rend.*, **190**, 1562 (1930).

[509] Darzens and Lévy, *Compt. rend.*, **194**, 2056 (1932).

[510] Darzens and Lévy, *Compt. rend.*, **199**, 1426 (1934).

[511] Darzens and Lévy, *Compt. rend.*, **200**, 469 (1935).

[512] Darzens and Lévy, *Compt. rend.*, **200**, 2187 (1935).

[513] Darzens and Lévy, *Compt. rend.*, **201**, 730 (1935).

[514] Darzens and Lévy, *Compt. rend.*, **202**, 427 (1936).

[515] Darzens and Lévy, *Compt. rend.*, **203**, 669 (1936).

[516] Campbell and Wang, *J. Chem. Soc.*, **1949**, 2186.

methods[517-520] requires as intermediates suitably substituted allylmalonic esters.
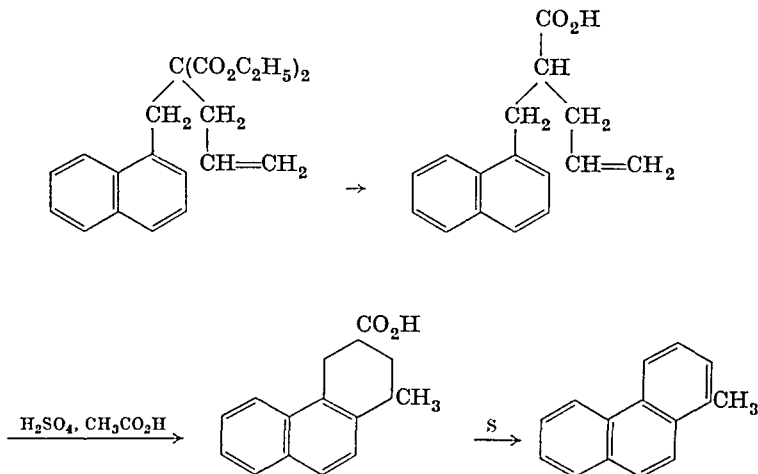
Lactones are readily prepared by the treatment of epoxides with the metal enolates of malonic esters,[8,11,12,282,521-527] cyanoacetic esters,[528] or ethyl isobutyrate.[69] Similarly, mononitriles are converted to cyclic imido esters,[27,329] which may be hydrolyzed to lactones.[25] The reaction of α-bromoisobutyraldehyde with diethyl malonate produced an unsaturated lactone rather than a normal alkylation product.[529]

[517] Tatevosyan and Vardanyan, *Zhur. Obshcheĭ Khim.* (*J. Gen. Chem. U.S.S.R.*), 19, 327 (1949) [*C. A.*, 43, 6609 (1949)].

[518] Tatevosyan and Vardanyan, *Zhur. Obshcheĭ Khim.* (*J. Gen. Chem. U.S.S.R.*), 19, 332 (1949) [*C. A.*, 43, 6609 (1949)].

[519] Tatevosyan and Vardanyan, *Zhur. Obshcheĭ Khim.* (*J. Gen. Chem. U.S.S.R.*), 21, 1170 (1951) [*C. A.*, 46, 2036 (1952)].

[520] Tatevosyan and Vardanyan, *Zhur. Obshcheĭ Khim.* (*J. Gen. Chem. U.S.S.R.*), 21, 1238 (1951) [*C. A.*, 46, 2037 (1952)].

[521] Traube and Lehmann, *Ber.*, 32, 720 (1899).

[522] Traube and Lehmann, *Ber.*, 34, 1971 (1901).

[523] Rothstein, *Bull. soc. chim. France*, [5] 2, 1936 (1935).

[524] Rothstein and Ficini, *Compt. rend.*, 234, 1293 (1952).

[525] Rothstein and Ficini, *Compt. rend.*, 234, 1694 (1952).

[526] Russell and VanderWerf, *J. Am. Chem. Soc.*, 69, 11 (1947).

[527] Cavallito, Fruehauf, and Bailey, *J. Am. Chem. Soc.*, 70, 3724 (1948).

[528] Glickman and Cope, *J. Am. Chem. Soc.*, 67, 1012 (1945).

[529] Franke and Groeger, *Monatsh. Chem.*, 43, 55 (1922).

In the synthesis of barbituric acids, malonic esters,[15,35,125,126,129,144,203,278,334,376,379,484,530-561] cyanoacetic esters,[562,563] and malononitriles[211] have found extensive use. The barbituric acids are formed when one of the aforementioned active methylene compounds is treated with urea or guanidine[563] in the presence of a base. The thiobarbituric acids[35,126,552-555] have been prepared from thiourea in an analogous manner. The intermediate imino com-

$$R_2C(CO_2C_2H_5)_2 + NH_2CONH_2 \xrightarrow{NaOC_2H_5} R_2C \begin{array}{c} CO-NH \\ | \quad\quad | \\ \quad\quad CO \\ | \quad\quad | \\ CO-NH \end{array} + 2C_2H_5OH$$
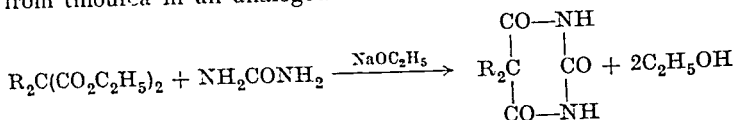
pounds formed in the reaction of substituted cyanoacetic esters or substituted malononitriles with urea or a urea derivative have been hydrolyzed with aqueous acid.

530 Reichert and Wilke, *Arch. Pharm.*, **276**, 596 (1938).

531 Tanaka, Miyanaga, and Okami, *Bull. Hyg. Research Inst. Japan*, **35**, 105 (1929) [*C. A.*, **24**, 1086 (1930)].

532 Tiffeneau, *Bull. soc. chim. France*, [4] **33**, 183, (1923).

533 Wichterle and Němeček, *Chem. Listy*, **37**, 105 (1943) [*C. A.*, **44**, 5815 (1950)].

534 Morsman, *Helv. Chim. Acta*, **18**, 1254 (1935).

535 Renard and Dony, *Ind. chim. belge*, **16**, 479 (1951) [*C. A.*, **46**, 10108 (1952)].

536 Shonle and Moment, *J. Am. Chem. Soc.*, **45**, 243 (1923).

537 Dox and Yoder, *J. Am. Chem. Soc.*, **45**, 1757 (1923).

538 Dox, *J. Am. Chem. Soc.*, **46**, 1707 (1924).

539 Dox, *J. Am. Chem. Soc.*, **46**, 2843 (1924).

540 Volwiler, *J. Am. Chem. Soc.*, **47**, 2236 (1925).

541 Cretcher, Koch, and Pittenger, *J. Am. Chem. Soc.*, **47**, 3083 (1925).

542 Hill and Keach, *J. Am. Chem. Soc.*, **48**, 257 (1926).

543 Dox and Jones, *J. Am. Chem. Soc.*, **50**, 2033 (1928).

544 Kirner and Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).

545 Volwiler and Tabern, *J. Am. Chem. Soc.*, **52**, 1676 (1930).

546 Keach, *J. Am. Chem. Soc.*, **55**, 2975 (1933).

547 Shonle and Waldo, *J. Am. Chem. Soc.*, **55**, 4649 (1933).

548 Hooper and Johnson, *J. Am. Chem. Soc.*, **56**, 484 (1934).

549 Kleiderer and Shonle, *J. Am. Chem. Soc.*, **56**, 1772 (1934).

550 Shonle, Waldo, Keltch, and Coles, *J. Am. Chem. Soc.*, **58**, 585 (1936).

551 Shonle and Doran, *J. Am. Chem. Soc.*, **58**, 1358 (1936).

552 Doran and Shonle, *J. Am. Chem. Soc.*, **59**, 1625 (1937).

553 Walter, Goodson, and Fosbinder, *J. Am. Chem. Soc.*, **67**, 659 (1945).

554 Walter, Goodson, and Fosbinder, *J. Am. Chem. Soc.*, **67**, 661 (1945).

555 Skinner and Mitchell, *J. Am. Chem. Soc.*, **67**, 1252 (1945).

556 van Tamelen and Van Zyl, *J. Am. Chem. Soc.*, **72**, 2979 (1950).

557 Walton, Doczi, and King, *J. Am. Chem. Soc.*, **72**, 4319 (1950).

558 Skinner and Huber, *J. Am. Chem. Soc.*, **73**, 3321 (1951).

559 Maynert, *J. Biol. Chem.*, **195**, 403 (1952).

560 Ohara, Tamura, Ohmori, and Mochizuki, *J. Pharm. Soc. Japan*, **71**, 911 (1951) [*C. A.*, **46**, 4548 (1952)].

561 Tatevosyan and Tuteryan, *Zhur. Priklad. Khim. (J. Applied Chem. U.S.S.R.)*, **20**, 287 (1947) [*C. A.*, **43**, 1725 (1949)].

562 Conrad, *Ann.*, **340**, 310 (1905).

563 Cope and Hancock, *J. Am. Chem. Soc.*, **61**, 776 (1939).

EXPERIMENTAL CONDITIONS AND PROCEDURES

If optimum yields are to be obtained from an alkylation reaction the apparatus, solvent, and reactants must be anhydrous. Although the maintenance of an inert (nitrogen) atmosphere in the reaction is advisable, this precaution is of prime importance if a high-boiling solvent is used or if the reaction is run at a temperature below the boiling point of the solvent. Without protection from the atmosphere afforded by solvent vapor or by an inert gas, many of the alkoxides and enolates are rapidly attacked by molecular oxygen.

If the alkylating agent is relatively volatile an excess of the reagent must be employed if the reaction is to go to completion. In such instances a desirable alternative is the use of dimethyl sulfate, diethyl sulfate, or the appropriate alkyl sulfonate. Although the completion of an alkylation can sometimes be determined by allowing the reaction to proceed until the reaction mixture becomes neutral, in many reactions complete neutrality is never reached. To determine the extent of alkylation in such cases it is advisable to remove aliquots of the reaction mixture periodically and to titrate them with a standard acid. To simplify subsequent extraction procedures the majority of the alcohol should be distilled from an alkylation reaction mixture before the mixture is poured into water.

Monoalkylmalonic esters must be boiled with 50% aqueous potassium hydroxide for two hours to effect saponification,[82,571] and dialkylmalonic esters require ten hours under similar conditions.[82,571] With less concentrated alkali longer reaction periods are required. The cyanoacetic esters are more rapidly hydrolyzed, the ester group of ethyl methylcyanoacetate being saponified almost instantly with 10% aqueous sodium hydroxide.[568] Similarly, ethyl dimethylcyanoacetate is saponified within twenty minutes.[568]

The ease with which alkylidenecyanoacetic esters form water-soluble sodium bisulfite adducts permits these esters to be separated from their alkylation products, which do not react with sodium bisulfite.[37,64,214,344] Unchanged alkylidenemalonic esters also may be removed by treatment with aqueous ammonium hydroxide. Under such conditions the alkylidene derivative is converted to the aldehyde or ketone and malonic ester in a reverse aldol reaction. The malonic ester so formed is converted to malonamide.[63]

Diethyl n-Butylmalonate.[13] This *Organic Syntheses* procedure illustrates the standard method used for the alkylation of malonic and cyanoacetic esters. The monoalkylated product is obtained in 80–90% yield from 5.15 moles of diethyl malonate and 5.0 moles of n-butyl bromide in the presence of ethanolic sodium ethoxide prepared from 2.5 l. of ethanol and 5 gram atoms of sodium.

Diethyl Benzylmalonate.[136] If the standard alkylation procedure for malonic esters (cf. diethyl n-butylmalonate, above) is applied to a reactive halide such as benzyl chloride, diethyl benzylmalonate is obtained in 51–57% yield, the remainder of the product being diethyl dibenzylmalonate.[119] In the procedure of Leuchs an excess of diethyl malonate is used to reduce dialkylation (p. 122).

To an ethanolic solution of diethyl sodiomalonate prepared from 11.5 g. (0.5 gram atom) of sodium, 150 ml. of absolute ethanol, and 160 g. (1.0 mole) of diethyl malonate, is added dropwise, with stirring, 63.2 g. (0.5 mole) of benzyl chloride. The reaction mixture is boiled under reflux until it is neutral to litmus. After most of the ethanol has been distilled from the mixture under reduced pressure, water is added to the residual oil and the mixture is extracted with ether. The ether solution is dried and fractionally distilled. The diethyl benzylmalonate, collected at 163–170°/12 mm., amounts to 107 g. (85%).

Diethyl Ethyl(phenyl)malonate (Inverse Addition Procedure).[42] In a 2-l. three-necked flask equipped with a dropping funnel, a mechanical stirrer, and an efficient reflux condenser connected to a trap chilled in solid carbon dioxide are placed 264 g. (1.1 moles) of diethyl phenylmalonate

[171] Norris and Tucker, *J. Am. Chem. Soc.*, **55**, 4697 (1933).

and 131 g. (1.2 moles) of ethyl bromide. While the contents of the flask are maintained at 45°, a solution of sodium ethoxide, prepared by the addition of 25 g. (1.1 gram atoms) of sodium to 450 ml. of absolute ethanol and followed by dilution of the solution with 10 ml. of ethyl acetate, is added dropwise with stirring. The sodium ethoxide solution is added at such a rate that the reaction mixture never becomes more than slightly basic to moist phenolphthalein paper. Near the end of the addition period any ethyl bromide which has collected in the solid carbon dioxide trap is returned to the reaction vessel. After the addition is complete (time required one and one-half to two hours) the reaction mixture is heated to 45° with stirring for one hour, and then the bulk of the ethanol is distilled from the reaction mixture. After water has been added to the residual oil and the mixture extracted with ether, the ether solution is dried over sodium sulfate and fractionally distilled. The diethyl ethyl-(phenyl)malonate is collected at 166–168°/12–13 mm.; yield 248 g. (97%).

Diethyl Ethyl(isopropyl)malonate. (*A*) *Alkylation of Diethyl Ethyl-malonate.*[145] To a solution of the sodium enolate of diethyl ethylmalonate, prepared from 24.8 g. (1.08 gram atoms) of sodium, 300 ml. of absolute ethanol, and 200 g. (1.08 moles) of diethyl ethylmalonate, 190 g. (1.12 moles) of isopropyl iodide is added dropwise. After the reaction mixture has been boiled under reflux with stirring for fifteen hours, most of the ethanol is distilled from the mixture and water is added. The product is extracted with ether, and the ether solution is dried over calcium chloride and fractionally distilled. The yield of diethyl ethyl(isopropyl)-malonate, b.p. 230–235°, is 113 g. (46%). If the lower-boiling fractions are realkylated, the yield of diethyl ethyl(isopropyl)malonate may be raised to 75%.

diethyl ethyl(isopropyl)malonate, collected at 112–115°/18 mm., amounts to 150 g. (65%).

Diethyl Isopropyl(formamido)malonate.[246] Diethyl formamido-malonate[572] (11.5 g., 0.056 mole) is added in small portions to 1.44 g. (0.06 mole) of sodium hydride in 25 g. of anhydrous dimethylformamide. After the mixture has been allowed to stand for thirty minutes it is filtered and the filtrate is treated with 12.3 g. (0.10 mole) of isopropyl bromide. The resulting mixture is boiled under reflux for two hours, and then most of the solvent is removed by distillation under reduced pressure. The residue is mixed with 125 ml. of water and allowed to stand in an ice bath until the oil that initially separates has solidified. The crude product is collected on a filter, washed with water, dried, and recrystallized from an ether-petroleum ether mixture. The yield of diethyl isopropyl(forma-mido)malonate, m.p. 67–73°, is 6.95 g. (50%). An additional recrystallization raises the melting point to 73.5–74°.

Diethyl 1,1-Cyclobutanedicarboxylate.[573] A solution of sodium ethoxide is prepared by the addition of 23 g. (1 gram atom) of sodium to 500 ml. of absolute ethanol contained in a three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a long-stemmed dropping funnel. A 200-ml. portion of the solution is drawn into the dropping funnel with suction, and the dropping funnel is attached to the top of the reflux condenser. Diethyl malonate (96 g., 0.6 mole) is then added to the flask, and the mixture is heated to boiling with stirring. Over a period of one hour the sodium ethoxide solution and 101 g. (0.5 mole) of tri-methylenebromide are added concurrently to the boiling reaction mixture. After the addition is complete the mixture is boiled under reflux with stirring for ninety minutes, and then about 400 ml. of ethanol is distilled from the reaction mixture. The residue is mixed with water and extracted with three portions of benzene. After the benzene has been distilled from the extract the residue is distilled under reduced pressure. The diethyl 1,1-cyclobutanedicarboxylate, collected at 105–112°/15 mm., amounts to 60–65 g. (60–67%).

Ethyl α-Ethyl-α-methylvalerate.[68] Ethyl α-methylbutyrate (23.5 g., 0.18 mole) is added to an ethereal solution containing 0.18 mole of sodium triphenylmethide. After the reaction mixture has been shaken for five minutes, 30.7 g. (0.18 mole) of n-propyl iodide is added, and the reaction flask is stoppered, shaken, and allowed to stand overnight. The ethereal solution is washed with 200 ml. of water and dried, first over sodium sulfate and then over anhydrous calcium sulfate ("Drierite"). After the ether has been removed, the residue is distilled and the crude ester is

[572] Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).
[573] Cason and Allen, *J. Org. Chem.*, **14**, 1036 (1949).

of ethyl *n*-butylcyanoacetate.   After the mixture has been stirred for five minutes, 73.8 g. (0.6 mole) of isopropyl bromide is added during a period of two minutes.   The mixture is boiled under reflux with stirring for three hours, and then about 200 ml. of ethanol is distilled from the mixture under reduced pressure.   The residue is diluted with 3 volumes of water, acidified by addition of a few drops of hydrochloric acid, and extracted with three portions of benzene.   The combined benzene extracts are washed with water and distilled.   The crude ester, b.p. 113–115°/6 mm., is shaken with 160 ml. of 5% aqueous sodium hydroxide for one and one-half hours to hydrolyze any unchanged monoalkyl ester present.   The ester is extracted with ether, and the extract is washed with water, diluted with benzene, and distilled.   The pure ethyl *n*-butyl(isopropyl)cyano-acetate is collected at 115–116°/7 mm., n_D^{25} 1.4327, yield 91.5 g. (87%).

α-Cyclohexylphenylacetonitrile.[576]   This *Organic Syntheses* procedure illustrates the alkylation of a mononitrile in the presence of sodium amide. The reaction of a suspension in toluene of the sodium enolate of phenyl-acetonitrile (prepared in liquid ammonia from 0.35 mole of phenylaceto-nitrile and 0.35 mole of sodium amide) with 0.40 mole of cyclohexyl bromide produces α-cyclohexylphenylacetonitrile in 65–77% yield.

TABULAR SURVEY OF THE ALKYLATION OF ESTERS AND NITRILES

The compounds listed in Tables I to XV have been arranged according to the nature of the active methylene compound.   Malonic esters precede cyanoacetic esters, which in turn are followed by monocarboxylic esters and mononitriles.   In Tables XVI to XX are surveyed several alternative methods of alkylation.   Within each table the compounds are listed in order of increasing number of carbon atoms, monoalkyl derivatives preceding dialkyl derivatives.   Among the monoalkyl derivatives acyclic groups are found first, followed in turn by saturated carbocyclic, aromatic, and then heterocyclic substituents.   The straight-chain alkyl derivatives have been placed before branched-chain derivatives, the latter groups being listed in order of increased branching; the unsaturated substituents follow.   Monocyclic precede bicyclic derivatives, the isomers with the smallest rings always being listed first.   Oxygen heterocycles will be found before heterocycles containing sulfur.   Next are listed the nitrogen heterocycles, followed by substituents containing two or more hetero atoms.

The alkylating agents employed have also been arranged in the order of increasing number of carbon atoms.   Within a group of alkylating agents with the same number of carbon atoms the order of arrangement is

[576] Hancock and Cope, *Org. Syntheses*, **25**, 25 (1945).

chlorides, bromides, iodides, unsaturated halides, carbonates, sulfates, sulfonates, dihalides, and epoxides. Ethers have been placed just after their hydrocarbon analogs. For example, $n\text{-}C_3H_7O(CH_2)_3Br$ would follow $n\text{-}C_6H_{13}Br$, and p-methoxybenzyl bromide would follow p-methylbenzyl bromide.
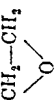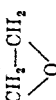
In those reactions where more than one reference is cited the experimental data are taken from the first reference, the remaining references being arranged in numerical order. Where two figures are listed in the column headed "Yield" the first figure refers to the actual yield or conversion, and the second, enclosed in parentheses, is based on the amount of starting material consumed. In cases listed in the tables in which a compound resulting from hydrolysis, decarboxylation, or some other transformation was isolated rather than the initial alkylation product, the formula of the product actually isolated is listed and the yield cited is the yield of that compound. The literature has been reviewed through 1952 with the occasional inclusion of more recent work.

Because of the extent of the literature on alkylation and complexity of searching this literature by subject, there are undoubtedly many examples of alkylation that were not found. To avoid confusion in the nomenclature of disubstituted active methylene compounds with unlike substituents attached to the same carbon atom one of the groups is enclosed in parentheses. For example the ester $C_2H_5C(C_6H_5)(CO_2C_2H_5)_2$ would be named diethyl ethyl(phenyl)malonate.

TABLE I

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
I_2	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	100	$NaOC_2H_5$	Ethanol–ether	260, 107, 261
I_2	$(C_2H_5O_2C)_2C=C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	260
C_1					
CH_3Br	$CH_3CH(CO_2C_2H_5)_2$	79–83	$NaOC_2H_5$	Ethanol	570
CH_3I	$CH_3CH(CO_2C_2H_5)_2$	94	$NaOC_2H_5$	Ethanol	169, 280, 577–582
CH_3I	$CH_3CH(CO_2C_2H_5)_2$	82	KOH	None	82
CH_3I	$CH_3CH(CO_2C_2H_5)_2$	—	Na	None	583
$(CH_3)_2SO_4$	$CH_3CH(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	336
$p\text{-}CH_3C_6H_4SO_3CH_3$	$CH_3CH(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	335
CH_2Cl_2	$(C_2H_5O_2C)_2CHCH_2CH(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	293, 294
CH_2I_2	$(C_2H_5O_2C)_2CHCH_2CH(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	Ethanol	296, 297, 298
$CHCl_3$	$(C_2H_5O_2C)_2CHCH=C(CO_2C_2H_5)_2$	56	$NaOC_2H_5$	Ethanol	221, 584–587
CCl_4	$(C_2H_5O_2C)_2CHCH=C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	588, 172, 589, 590
CBr_4	$(C_2H_5O_2C)_2CHCH=C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	591, 590
CCl_3NO_2	$(C_2H_5O_2C)_2CHCH=C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	591, 590
C_2					
C_2H_5Br	$C_2H_5CH(CO_2C_2H_5)_2$	80	Na	None	280
C_2H_5Br	$C_2H_5CH(CO_2C_2H_5)_2$	90–94	$NaOC_2H_5$	Ethanol	536, 545
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$	83	$NaOC_2H_5$	Ethanol	399, 433, 540, 541, 592–594
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$ and $(C_2H_5)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	595

Alkylating agent	Compound	Yield %	Base	Solvent	References
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$	—	$Mg(OC_2H_5)_2$	Ethanol	596
C_2H_5I	$(C_2H_5)_2C(CO_2C_2H_5)_2$	Good	$Mg(OC_2H_5)_2$	Ethanol	56
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$	60	KOH	None	82
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$	Poor	Ag_2O	None	96
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$	75	Na	None	280
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$	100	Zn	None	597, 598
C_2H_5I	$(C_2H_5)_2C(CO_2C_2H_5)_2$	100	Zn	None	507, 94, 599
C_2H_5I	$C_2H_5CH(CO_2C_2H_5)_2$	—	$MgHg_x$	C_6H_6	596
$(C_2H_5)_2SO_4$	$C_2H_5CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	249
$(C_2H_5)_2SO_4$	$C_2H_5CH(CO_2C_2H_5)_2$	59	$Mg(OC_2H_5)_2$	Ethanol	220
$p\text{-}CH_3C_6H_4SO_3C_2H_5$	$C_2H_5CH(CO_2C_2H_5)_2$	68	$NaOC_2H_5$	Ethanol	335
$ClCH_2CH_2Cl$	$(C_2H_5O_2C)_2CH(CH_2)_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	268
CH_2ClCH_2Cl	$(C_2H_5O_2C)_2CH(CH_2)_2CH(CO_2C_2H_5)_2$, $C_2H_5O_2CCH_2(CH_2)_2CH(CO_2C_2H_5)_2$, and $C_2H_5O_2CCH_2(CH_2)_2CH_2CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	600
CH_2BrCH_2Br	$BrCH_2CH_2CH(CO_2C_2H_5)_2$	35–40	Na	C_6H_6	54
CH_2BrCH_2Br	$BrCH_2CH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	601
CH_2BrCH_2Br	$(C_2H_5O_2C)_2CH(CH_2)_2CH(CO_2C_2H_5)_2$	27–30	Na	Toluene	602
CH_2BrCH_2Br	$(C_2H_5O_2C)_2CH(CH_2)_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	603, 266
CH_2BrCH_2Br	$(C_2H_5O_2C)_2CH(CH_2)_2CH(CO_2C_2H_5)_2$	$\{60\text{–}65\ (65\text{–}70)\}$	$Mg(OC_2H_5)_2$	Ethanol	602
CH_2BrCH_2Br	cyclopropane: $\mathrm{CH_2}{\diagdown}\ {\diagup}\mathrm{CH_2}\ C(CO_2C_2H_5)_2$	40	$NaOC_2H_5$	Ethanol	484, 485, 488, 604
$BrCH_2OCH_2Br$	$(C_2H_5O_2C)_2CHCHCH_2OCH_2CH(CO_2C_2H_5)_2$	35	$Mg(OC_2H_5)_2$	Ethanol	219
CH_2ClCH_2OH	$HOCH_2CH_2CH(CO_2C_2H_5)_2$ $OC{-}\!-\!{-}O$	60	$NaOC_2H_5$	Ethanol	605, 148
CH_2ClCH_2OH	$CH_2CH_2CCH_2CH_2$ / $O{-}\!-\!{-}CO$	5–10	$NaOC_2H_5$	Ethanol	606

Note: References 577–1080 are on pp. 322–331.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
CH_2BrCH_2OH	$CH_2CH_2CCH_2CH_2$ (lactone ring structure)	5–10	$NaOC_2H_5$	Ethanol	606
$CH_2ClCH_2O_2CCH_3$	$CH_2CH_2CCH_2CH_2$ (lactone ring structure)	5–10	$NaOC_2H_5$	Ethanol	606
$CH_2BrCH_2O_2CCH_3$	$CH_2CH_2CCH_2CH_2$ (lactone ring structure)	—	$NaOC_2H_5$	Ethanol	606, 607
$CH_2{-}CH_2$ (epoxide)	$HOCH_2CH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	521
$CH_2{-}CH_2$ (epoxide)	α-Carbethoxybutyrolactone	—	$NaOC_2H_5$	Ethanol	522
CH_3CCl_3	None	—	$NaOC_2H_5$	Ethanol	608
CH_3OCH_2Cl	$CH_3OCH_2CH(CO_2C_2H_5)_2$	49	Na	Ether	204, 542, 609
CH_3SCH_2Cl	$CH_3SCH_2CH(CO_2C_2H_5)_2$*	9	Na	Ether	205
$ClCH_2CN$	$NCCH_2CH(CO_2C_2H_5)_2$	30	Na	C_6H_6	610

C_3

Halide	Product	%	Condensing agent	Solvent	References
$n\text{-}C_3H_7Br$	$n\text{-}C_3H_7CH(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	611, 541
$n\text{-}C_3H_7Br$	$n\text{-}C_3H_7CH(CO_2C_2H_5)_2$	80	Na	None	280
$n\text{-}C_3H_7Br$	$(n\text{-}C_3H_7)_2C(CO_2C_2H_5)_2$	30	$NaOC_2H_5$	Ethanol	612
$n\text{-}C_3H_7I$	$n\text{-}C_3H_7CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	613, 50, 540
$n\text{-}C_3H_7I$	$n\text{-}C_3H_7CH(CO_2C_2H_5)_2$	—	Zn	None	614
$n\text{-}C_3H_7I$	$(n\text{-}C_3H_7)_2C(CO_2C_2H_5)_2$	33	$NaOC_2H_5$	Ethanol	612
$n\text{-}C_3H_7I$	$(n\text{-}C_3H_7)_2C(CO_2C_2H_5)_2$	—	Zn	None	614
$C_2H_5OCH_2Cl$	$(C_2H_5OCH_2)_2C(CO_2C_2H_5)_2$	25	Na	Ether	542
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2CH(CO_2C_2H_5)_2$	—	Na	Ether	205
$CH_3O(CH_2)_2I$	$\begin{array}{c}CH_2CH_2CCH_2CH_2\\ \mid\qquad\qquad\mid\\ OC\text{——}O\\ \mid\qquad\qquad\mid\\ O\text{——}CO\end{array}$	40	$NaOC_2H_5$	Ethanol	606
$CH_3CH(OCH_3)Cl$	$CH_3CH(OCH_3)CH(CO_2C_2H_5)_2$	70	Na	Ether	535
$i\text{-}C_3H_7Cl$	$i\text{-}C_3H_7CH(CO_2C_2H_5)_2$	100	$NaOC_2H_5$	Ethanol	87
$i\text{-}C_3H_7Br$	$i\text{-}C_3H_7CH(CO_2C_2H_5)_2$	95	$NaOC_2H_5$	Ethanol	169, 47, 387, 545
$i\text{-}C_3H_7Br$	$i\text{-}C_3H_7CH(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	$(C_2H_5)_2CO$	227, 51
$i\text{-}C_3H_7I$	$i\text{-}C_3H_7CH(CO_2C_2H_5)_2$	77	Na	None	280
$i\text{-}C_3H_7I$	$i\text{-}C_3H_7CH(CO_2C_2H_5)_2$	63	$NaOC_2H_5$	Ethanol	577, 569
$i\text{-}C_3H_7I$	$i\text{-}C_3H_7CH(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	540, 35, 571, 615
$CH_2\text{=}CHCH_2Br$	$CH_2\text{=}CHCH_2CH(CO_2C_2H_5)_2$	91	$NaOC_2H_5$	Ethanol	121, 506, 571, 615–618
$CH_2\text{=}CHCH_2Br$	$CH_2\text{=}CHCH_2CH(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	$(C_2H_5O)_2CO$	51
$CH_2\text{=}CHCH_2Br$	$(CH_2\text{=}CHCH_2)_2C(CO_2C_2H_5)_2$	Good	$Mg(OC_2H_5)_2$	Ethanol	56
$CH_2\text{=}CHCH_2I$	$CH_2\text{=}CHCH_2CH(CO_2C_2H_5)_2$	85	$NaOC_2H_5$	Ethanol	619
$CH_2\text{=}CHCH_2I$	$(CH_2\text{=}CHCH_2)_2C(CO_2C_2H_5)_2$	100	$NaOC_2H_5$	Ethanol	619
$CH_2\text{=}CHCH_2I$	$(CH_2\text{=}CHCH_2)_2C(CO_2C_2H_5)_2$	—	Zn	None	620

Note: References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$p\text{-}CH_3C_6H_4SO_3CH_2CH_2CH_2CN$	$NCCH_2CH_2CH(CO_2C_2H_5)_2$	34	$NaOC_2H_5$	Ethanol	102
$F(CH_2)_3Br$	$F(CH_2)_3CH(CO_2C_2H_5)_2$	52	$NaOCH_3$	Ethanol	285
$ClCH{=}CHCH_2Cl$	$\{ClCH{=}CHCH_2CH(CO_2C_2H_5)_2$ / $(ClCH{=}CHCH_2)_2C(CO_2C_2H_5)_2$	26 / 32	$NaOC_2H_5$	Ethanol	621
$Cl(CH_2)_3Br$	$Cl(CH_2)_3CH(CO_2C_2H_5)_2$	93	$NaOC_2H_5$	Ethanol-ether	622, 480, 490, 623
$Cl(CH_2)_3Br$	$[Cl(CH_2)_3]_2C(CO_2C_2H_5)_2$	62	$NaOC_2H_5$	Ethanol	623, 624
$Cl(CH_2)_3Br$	Diethyl cyclobutane-1,1-dicarboxylate	8–10	$NaOC_2H_5$	Ethanol	624
$Cl(CH_2)_3Br$	Diethyl cyclobutane-1,1-dicarboxylate	55†	$NaOC_2H_5$	Ethanol	170, 625
$Cl(CH_2)_3I$	$I(CH_2)_3CH(CO_2C_2H_5)_2$	38	$NaOC_2H_5$	Ethanol	92
$Br(CH_2)_3Br$	$Br(CH_2)_3CH(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	131, 136, 627–629
$Br(CH_2)_3Br$	$(C_2H_5O_2C)_2CH(CH_2)_3CH(CO_2C_2H_5)_2$	15	$NaOC_2H_5$	Ethanol	131, 172, 267, 630–632
$Br(CH_2)_3Br$	Diethyl cyclobutane-1,1-dicarboxylate	60–65	$NaOC_2H_5$	Ethanol	573, 160, 172, 266, 483, 488, 491, 627, 633
$CH_3CHBrCH_2Br$	$\begin{array}{c} H_3CCH \\ \mid \quad\;\; \rangle C(CO_2C_2H_5)_2 \\ CH_2 \end{array}$	—	$NaOC_2H_5$	Ethanol	336, 626
CH_3COCH_2Br	$\{CH_3COCH_2CH(CO_2C_2H_5)_2$ / $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	70 / —	Na	Ether	593, 634
CH_3COCH_2Br	$CH_3COCH_2CH(CO_2C_2H_5)_2$	20	$NaOC_2H_5$	Ethanol	593, 634
$CH_3O_2CCH_2Cl$	$CH_3O_2CCH_2CH(CO_2CH_3)_2{*}$	27	$NaOCH_3$	CH_3OH	635

$CH_2CH_2CCl_3$	$CH_2{=}CClCH_2CH(CO_2C_2H_5)_2$	22	$NaOC_2H_5$	Ethanol	636
$CH_2{=}CHCH_2Cl$	α-Carbethoxy-δ-chloro-γ-valerolactone	78	$NaOC_2H_5$	Ethanol	136, 522
CH_2—$CHCH_2Cl$ (O)	$ClCH_2CHOHCH_2CH(CONH_2)_2$	—	$NaOC_2H_5$	Ethanol	521
CH_2—$CHCH_2Cl$ (O)	$CH_2OHCHOHCH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	637
$CH_2OHCHOHCH_2Cl$ $CH_2BrCHBrCH_2Br$	$CH_2{=}CBrCH_2CH(CO_2C_2H_5)_2$ and $(CH_2{=}CBrCH_2)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	638, 639
C_4					
n-C_4H_9Br	n-$C_3H_7CH(CO_2C_2H_5)_2$	80–90	$NaOC_2H_5$	Ethanol	13, 121, 142, 540, 541, 640, 641
n-C_4H_9I	n-$C_3H_7CH(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	399, 141
n-$C_3H_7OCH_2Cl$	n-$C_3H_7OCH_2CH(CO_2C_2H_5)_2$	21	Na	Ether	542
n-$C_3H_7OCH_2Cl$	$(n$-$C_3H_7OCH_2)_2C(CO_2C_2H_5)_2$	21	Na	Ether	542
$C_2H_5SO_3(CH_2)_2OC_2H_5$	$C_2H_5O(CH_2)_2CH(CO_2C_2H_5)_2$	65	$NaOC_2H_5$	Ethanol	646
i-C_4H_9Br	i-$C_4H_9CH(CO_2C_2H_5)_2$	77	$NaOC_2H_5$	Ethanol	427, 540, 555, 642
sec-C_4H_9Br	sec-$C_4H_9CH(CO_2C_2H_5)_2$	80–81	$NaOC_2H_5$	Ethanol	14, 148, 540, 571, 643, 645
sec-C_4H_9Br	$(sec$-$C_4H_9)_2C(CO_2C_4H_9$-$sec)_2$‡	78	$NaOC_4H_9$-sec $(sec$-$C_4H_9O)_2CO$	Ethanol	51
sec-C_4H_9I	sec-$C_4H_9CH(CO_2C_2H_5)_2$	88	$NaOC_2H_5$	Ethanol	582
$CH_3CH(OC_2H_5)Cl$	$CH_3CH(OC_2H_5)CH(CO_2C_2H_5)_2$	28	$NaNH_2$	C_6H_6-ether	203
$CH_3CH(OC_2H_5)Cl$	$CH_3CH(OC_2H_5)CH(CO_2C_2H_5)_2$	27	Na	Ether	535
t-C_4H_9Br	t-$C_4H_9CH(CO_2C_2H_5)_2$	6	$NaOC_2H_5$	Ethanol	15, 473
$CH_3CH{=}CHCH_2Cl$	$CH_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	18
$CH_3CH{=}CHCH_2Br$	$CH_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	647, 648

Note: References 577–1080 are on pp. 322–331.

• Dimethyl malonate was used in this experiment.

† The reactants were added in inverse order.

‡ Di-sec-butyl malonate was used in this experiment.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$CH_2{=}CH(CH_2)_2Br$	$CH_2{=}CH(CH_2)_2CH(CO_2C_2H_5)_2$	74	$NaOC_2H_5$	Ethanol	647
$CH_2{=}CHCH(CH_3)Cl$	$\{\,CH_2{=}CHCH(CH_3)CH(CO_2C_2H_5)_2$	54	$NaOC_2H_5$	Ethanol	18
	$CH_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$	2			552
$CH_2{=}C(CH_3)CH_2Br$	$CH_2{=}C(CH_3)CH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	
$\triangle$CHCH$_2$Br (cyclopropane, apex CH_2)	$\triangle$CHCH$_2$CH(CO$_2$C$_2$H$_5$)$_2$ (cyclopropane, apex CH_2)	66–70	$NaOC_2H_5$	Ethanol	649
$Cl(CH_2)_4Br$	$Cl(CH_2)_4CH(CO_2C_2H_5)_2$	65	$NaOC_2H_5$	Ethanol	431
$ClCH_2CH(CH_3)CH_2Br$	$ClCH_2CH(CH_3)CH_2CH(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	481, 482
$Br(CH_2)_4Br$	Diethyl cyclopentane-1,1-dicarboxylate	55	$NaOC_2H_5$	Ethanol	488, 308, 650
$CH_3CHBr(CH_2)_2Br$	Diethyl 2-methylcyclobutane-1,1-dicarboxylate	50–55§	$NaOC_2H_5$	Ethanol	160
$C_2H_5CHOHCHClCH_2Cl$	α-Carbethoxy-γ-ethyl-γ-butyrolactone	58	$NaOC_2H_5$	Ethanol	651
$C_2H_5OCHClCH_2Cl$	$(C_2H_5O_2C)_2C{=}CHCH_2CH(CO_2C_2H_5)_2$	69	Na	Ether	275
$C_2H_5OCHClCH_2Cl$	$ClCH_2CH(OC_2H_5)CH(CO_2C_2H_5)_2$	—	Na	Ether	275
$Cl(CH_2)_2O(CH_2)_2Cl$	Diethyl tetrahydropyran-4,4-dicarboxylate	26	$NaOC_2H_5$	Ethanol	496, 498
$CH_2{=}CHO(CH_2)_2Cl$	$[CH_2{=}CHO(CH_2)_2]_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	541
$I(CH_2)_2O(CH_2)_2I$	Diethyl tetrahydropyran-4,4-dicarboxylate	65	$NaOC_2H_5$	Ethanol	494
$n\text{-}C_3H_7SCH_2Cl$	$(n\text{-}C_3H_7SCH_2)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$C_2H_5SCH(CH_3)Cl$	$\{\,C_2H_5SCH(CH_3)CH(CO_2C_2H_5)_2$ and $[C_2H_5SCH(CH_3)]_2C(CO_2C_2H_5)_2$	55	$NaOC_2H_5$	Toluene	126
$CH_3CH{=}CHCHCl_2$	$ClCH{=}CHCH(CH_3)CH(CO_2C_2H_5)_2$	41	$NaOC_2H_5$	Ethanol	636
$CH_3CCl{=}CHCH_2Cl$	$CH_3CCl{=}CHCH_2CH(CO_2C_2H_5)_2$	62	$NaOC_2H_5$	Ethanol	533, 561, 652
$BrCH_2CH{=}CHCH_2Br$	$(C_2H_5O_2C)_2CHCH_2CH{=}CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	20

		Yield (%)	Base	Solvent	References
BrCH₂CH=CHCH₂Br	(C₂H₅O₂C)₂CHCH(CH=CH₂)·CH₂CH(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	20
BrCH₂CH=CHCH₂Br	CH₂=CHC(CO₂C₂H₅)₂ CH₂	56	NaOC₂H₅	Ethanol	20
CH₂=CHCH—CH₂ (O)	α-Carbethoxy-γ-vinyl-γ-butyrolactone	73	NaOC₂H₅	Ethanol	11, 526
CH₃OCH₂CH—CH₂ (O)	CH₃OCH₂CH—CH₂CH₂—O—CO	50–60	NaOC₂H₅	Ethanol	524
Cl(CH₂)₃CN	NC(CH₂)₃CH(CO₂C₂H₅)₂ ‖	75	NaOC₂H₅	Ether	132
ClCH₂CO₂C₂H₅	C₂H₅O₂CCH₂CH(CO₂C₂H₅)₂	—	Na	Ether	653
ClCH₂CO₂C₂H₅	C₂H₅O₂CCH₂CH(CO₂C₂H₅)₂	—	Na	C₆H₆	653, 161, 654
ClCH₂CO₂C₂H₅	C₂H₅O₂CCH₂CH(CO₂C₂H₅)₂	67	NaOC₂H₅	Ethanol	655, 594, 635
ClCH₂CO₂C₂H₅	(C₂H₅O₂CCH₂)₂C(CO₂C₂H₅)₂	87	Mg(OC₂H₅)₂	Ethanol	55
4-Chloromethylimidazole hydrochloride	Diethyl (4-imidazolemethyl)malonate	49	NaOC₂H₅	Ethanol	209
C_5					
n-C₅H₁₁Br	n-C₅H₁₁CH(CO₂C₂H₅)₂	70–85	NaOC₂H₅	Ethanol	545, 148, 543, 656
CH₃O(CH₂)₄Br	CH₃O(CH₂)₄CH(CO₂C₂H₅)₂	80–84	NaOC₂H₅	Ethanol	662
i-C₅H₁₁Br	i-C₅H₁₁CH(CO₂C₂H₅)₂	78	NaOC₂H₅	Ethanol	657, 35, 148, 540, 545, 555, 571, 616, 658
n-C₃H₇CH(CH₃)Br	n-C₃H₇CH(CH₃)CH(CO₂C₂H₅)₂	51	NaOC₂H₅	Ethanol	148, 659
sec-C₄H₉CH₂Br	sec-C₄H₉CH₂CH(CO₂C₂H₅)₂	70–85	NaOC₂H₅	Ethanol	545, 659
i-C₃H₇(CH₃)Br	i-C₃H₇(CH₃)CH(CO₂H)₂	83	NaOC₂H₅	Ethanol	138
(C₂H₅)₂CHBr	(C₂H₅)₂CHCH(CO₂C₂H₅)₂	36	NaOC₂H₅	Ethanol	148

Note: References 577–1080 are on pp. 322–331.
§ The product contained up to 18% of unsaturated material.
‖ The cyanide group has —C≡N.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$(+)\text{-}CH_3CH=CHCH(CH_3)Cl$	$rac\text{-}CH_3CH=CHCH(CH_3)CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	660
$CH_2=CH(CH_3)_2Br$	$CH_2=CH(CH_3)_2CH(CO_2C_2H_5)_2$	74	$NaOC_2H_5$	Ethanol	661
$(CH_3)_2C=CHCH_2Br$	$(CH_3)_2C=CHCH_2CH(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	666, 47, 616, 663
$HC\equiv CC(CH_3)_2Cl$	$HC\equiv CC(CH_3)_2CH(CO_2C_2H_5)_2$	45	$NaOC_2H_5$	Ethanol	664
$Br(CH_2)_3Br$	$\{[(C_2H_5O_2C)_2CH(CH_2)_3CH(CO_2C_2H_5)_2$ / Diethyl cyclohexano-1,1-dicarboxylate	— / 30	$NaOC_2H_5$	Ethanol	304 308,
$Br(CH_2)_3CH(CH_3)Br$	Diethyl 2-methylcyclopentane-1,1-dicarboxylate	—	$NaOC_2H_5$	Ethanol	665
$(CH_3)_2CBrCH(CH_3)_2Br$	$\{[(CH_3)_2C=CHCH_2CH(CO_2C_2H_5)_2$ / $[(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	56	$NaOC_2H_5$	Ethanol	318, 173, 616 667
$F(CH_2)_5Br$	$F(CH_2)_5CH(CO_2C_2H_5)_2$	74	$NaOCH_3$	Ethanol	285
$NC(CH_2)_4Br$	$NC(CH_2)_4CH(CO_2C_2H_5)_2$	56–59	$NaOC_2H_5$	Ethanol	668
$CH_3CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(CH_3)CH(CO_2C_2H_5)_2$	—	Na	—	161
$CH_3CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(CH_3)CH(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	223, 669
$Br(CH_2)_4CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_4CH(CO_2C_2H_5)_2$	58	$NaOC_2H_5$	Ethanol	610, 670
$Br(CH_2)_2CO_2C_2H_5$	$[(C_2H_5O_2C(CH_2)_2CH(CO_2C_2H_5)_2$ / $[C_2H_5O_2C(CH_2)_2]_2C(CO_2C_2H_5)_2$	58 / 28	$NaOC_2H_5$	Ethanol	671
$I(CH_2)_2CO_2C_2H_5$	$[C_2H_5O_2C(CH_2)_2]_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	672
$CH_2BrCHBrCO_2C_2H_5$	$CH_2{-}C(CO_2C_2H_5)_2$ / $CHCO_2C_2H_5$	77	$NaOC_2H_5$	Ethanol	673
$Br_2C=CHCO_2C_2H_5$	Not established	Poor	$NaOC_2H_5$	Ethanol	674

Reagent	Product	Yield %	Base	Solvent	References
$BrCH(CO_2CH_3)_2$	$(CH_3O_2C)_2CHCH(CO_2CH_3)_2{}^*$ $(CH_3O_2C)_2CHC(CO_2CH_3)_2CH(CO_2CH_3)_2{}^*$	—	$NaOCH_3$	CH_3OH	675
Cyclobutylmethyl tosylate	Diethyl (cyclobutylmethyl)malonate	Low	$NaOC_2H_5$	Ethanol	334
Cyclopentyl bromide	Diethyl cyclopentylmalonate	50	$NaOC_2H_5$	Ethanol	31, 148, 677
Cyclopentyl iodide	Diethyl cyclopentylmalonate	70	$NaOC_2H_5$	Ethanol	676
2-Cyclopentenyl chloride	Diethyl 2-cyclopentenylmalonate	50	Na	C_6H_6	287
2-Cyclopentenyl chloride	Diethyl 2-cyclopentenylmalonate	70	Na	Toluene	678, 151
2-Cyclopentenyl chloride	Diethyl 2-cyclopentenylmalonate	84–88	$NaOC_2H_5$	Ethanol	274, 286, 287, 679–681
trans-1,4-Dibromo-2-cyclopentene	Diethyl bicyclo-[3.1.0]-hex-2-ene-6,6-dicarboxylate	33	$NaOC_2H_5$	Ethanol	152
	Diethyl (ethoxycyclopentenyl)malonate (isomers)	14			
	$(C_2H_2O_2C)_2HC\!-\!\text{[cyclopentene]}\!-\!CH(CO_2C_2H_5)_2$	—			
cis-1,4-Dibromo-2-cyclopentene	Diethyl bicyclo-[3.1.0]-hex-2-ene-6,6-dicarboxylate	16	$NaOC_2H_5$	Ethanol	152
$C_2H_5OCH_2CH\!-\!CH_2$ over O	$C_2H_5OCH_2CHCH_2CHCO_2C_2H_5$ with $O\!-\!CO$ bridge	50–60	$NaOC_2H_5$	Ethanol	524
$H_5C_2C(CH_3)\!-\!CH_2$ over O	$H_5C_2C(CH_3)CH_2CHCO_2C_2H_5$ with $O\!-\!CO$ bridge	50–60	$NaOC_2H_5$	Ethanol	525
Cyclopentene oxide	trans-Diethyl (2-hydroxy-cyclopentyl)malonate	27	Na	C_6H_6	7
Cyclopentene oxide	trans-Diethyl (2-hydroxy-cyclopentyl)malonate	70–75	$NaOC_2H_5$	Ethanol	7
Tetrahydrofurfuryl bromide	Diethyl tetrahydrofurfurylmalonate	70	$NaOC_2H_5$	Ethanol	682
Furfuryl chloride	Diethyl furfurylmalonate	76	$NaOC_2H_5$	Ethanol	544
2-Chlorotetrahydropyran	Diethyl 2-tetrahydropyranylmalonate	—	NaH	Toluene	683

Note: References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_6					
$n\text{-}C_6H_{13}Br$	$n\text{-}C_6H_{13}CH(CO_2C_2H_5)_2$	80–85	$NaOC_2H_5$	Ethanol	282, 538
$n\text{-}C_6H_{13}Br$	$(n\text{-}C_6H_{13})_2C(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	121
$n\text{-}C_6H_{13}I$	$n\text{-}C_6H_{13}CH(CO_2C_2H_5)_2$	90	$NaOC_2H_5$	Ethanol	684
$n\text{-}C_6H_{13}I$	$(n\text{-}C_6H_{13})_2C(CO_2C_2H_5)_2$	92	$NaOC_4H_9\text{-}n$	$n\text{-}C_4H_9OH$	685
$CH_3O(CH_2)_3Br$	$CH_3O(CH_2)_3CH(CO_2C_2H_5)_2$	62	—	—	691
$C_2H_5O(CH_2)_3Br$	$C_2H_5O(CH_2)_3CH(CO_2C_2H_5)_2$	87	$NaOC_2H_5$	Ethanol	646
$n\text{-}C_4H_9CH(CH_3)Br$	$n\text{-}C_4H_9CH(CH_3)CH(CO_2C_2H_5)_2$	83	$NaOC_2H_5$	Ethanol	686
$i\text{-}C_3H_7(CH_2)_3I$	$i\text{-}C_3H_7(CH_2)_3CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	138
$n\text{-}C_3H_7CH(CH_3)CH_2Br$	$n\text{-}C_3H_7CH(CH_3)CH_2CH(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	555
$n\text{-}C_3H_7CH(C_2H_5)Br$	$n\text{-}C_3H_7CH(C_2H_5)CH(CO_2C_2H_5)_2$	55	$NaOC_2H_5$	Ethanol	35
$(C_2H_5)_2CHCH_2Br$	$(C_2H_5)_2CHCH_2CH(CO_2C_2H_5)_2$	80–85	$NaOC_2H_5$	Ethanol	282, 555, 687, 688
$(C_2H_5O)_2CHCH_2Br$	$(C_2H_5O)_2CHCH_2CH(CO_2C_2H_5)_2$	57	$NaOC_2H_5$	Ethanol	689
$t\text{-}C_4H_9(CH_2)_2Br$	$t\text{-}C_4H_9(CH_2)_2CH(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Ethanol	690
$C_2H_5CH(OCH_3)(CH_2)_2Cl\cdot KI$	$C_2H_5CH(OCH_3)(CH_2)_2CH(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	292
$trans\text{-}C_2H_5CH=CH(CH_2)_2Br$	$C_2H_5CH=CH(CH_2)_2CH(CO_2C_2H_5)_2$	65	$NaOC_2H_5$	Ethanol-toluene	692
$cis\text{-}C_2H_5CH=CH(CH_2)_2I$	$cis\text{-}C_2H_5CH=CH(CH_2)_2CH(CO_2C_2H_5)_2$	54	Not stated	—	693
$CH_2=CH(CH_2)_4Br$	$CH_2=CH(CH_2)_4CH(CO_2C_2H_5)_2$	73	$NaOC_2H_5$	Ethanol	210
$CH_3O(CH_2)_2CH=CHCH_2Cl$	$CH_3O(CH_2)_2CH=CHCH_2CH(CO_2C_2H_5)_2$	5	$NaOC_2H_5$	Ethanol	691
$CH_3O(CH_2)_2CH=CHCH_2Cl$	$\{[CH_3O(CH_2)_2CH=CHCH_2]_2C(CO_2C_2H_5)_2$	23	$Mg(OC_2H_5)_2$	Ethanol	694
$CH_3O(CH_2)_2CHClCH=CH_2$	$CH_3O(CH_2)_2CH=CHCH_2CH(CO_2C_2H_5)_2$	7	$NaOC_2H_5$	Ethanol	694

Halide	Product	Yield (%)	Condensing agent	Solvent	References
$CH_3O(CH_2)_2CHClCH{=}CH_2$	$\{CH_3O(CH_2)_2CH{=}CHCH_2CH(CO_2C_2H_5)_2$ $[CH_3O(CH_2)_2CH{=}CHCH_2]_2C(CO_2C_2H_5)_2\}$	29 5	$Mg(OC_2H_5)_2$	Ethanol	694
$n\text{-}C_3H_7C{\equiv}CCH_2Br$	$\{n\text{-}C_3H_7C{\equiv}CCH_2CH(CO_2C_2H_5)_2$ $[n\text{-}C_3H_7C{\equiv}CCH_2]_2C(CO_2C_2H_5)_2\}$	57 13	$NaOC_2H_5$	Ethanol	695
$CH_3CHBr(CH_2)_4Br$	$\{$Tetraethyl 2-methylheptane-1,1,7,7-tetracarboxylate Diethyl 2-methylcyclohexane-1,1-dicarboxylate$\}$	—	$NaOC_2H_5$	Ethanol	696
$CH_3CHBr(CH_2)_4Br$	$CH_3CHBr(CH_2)_4CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	210
$Br(CH_2)_8Br$	Diethyl cycloheptane-1,1-dicarboxylate and tetraethyl octane-1,1,8,8-tetracarboxylate	—	$NaOC_2H_5$	Ethanol	269
$C_2H_5C(CH_3)Br(CH_2)_2Br$	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$, and $C_2H_5C(CH_3){=}CHCH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	697, 318
$CH_3CO(CH_2)_4Br$	$CH_3CO(CH_2)_4CH(CO_2C_2H_5)_2$	74	$NaOC_2H_5$	Ethanol	698
$(CH_3)_2N(CH_2)_2CH(CH_3)Cl$	$(CH_3)_2N(CH_2)_2CH(CH_3)CH(CO_2C_2H_5)_2$	72	$NaOC_2H_5$	Ethanol	699
$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2CH(CO_2C_2H_5)_2$	45	Na	C_6H_6	610
$Br(CH_2)_3CN$	$NC(CH_2)_3CH(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	700
$C_2H_5CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_2H_5)CH(CO_2C_2H_5)_2$	—	Na	None	161
$C_2H_5CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_2H_5)CH(CO_2C_2H_5)_2$	55	$NaOC_2H_5$	Ethanol	223
$(CH_3)_2CBrCO_2C_2H_5$	$C_2H_5O_2CC(CH_3)_2CH(CO_2C_2H_5)_2$	—	Na	None	161
$(CH_3)_2CBrCO_2C_2H_5$	$C_2H_5O_2CC(CH_3)_2CH(CO_2C_2H_5)_2$ $CHCO_2CH_3$	60	$NaOC_2H_5$	Ethanol	701, 223, 702
$CH_3O_2CCHBrCHBrCO_2CH_3$	$CH_3O_2CCHBr{-}C(CO_2CH_3)_2$*	80–90	$NaOHC_3$	Methanol	175, 703
Cyclohexyl bromide	Diethyl cyclohexylmalonate	60	$NaOC_2H_5$	Ethanol	35, 31, 50, 149, 286, 704, 705
Cyclohexyl bromide	Di-t-butyl cyclohexylmalonate¶	77	NaH	$t\text{-}C_4H_9OH$	393
1-Chloro-2-cyclohexene	Diethyl 2-cyclohexenylmalonate	—	—	—	150

Note: References 557–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

¶ Di-t-butyl malonate was used in this experiment.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
1,2-Dichlorocyclohexane	Diethyl 2-cyclohexenylmalonato	<60	$NaOC_2H_5$	Ethanol	150
1-Chloro-2-bromocyclohexane	Diethyl 2-cyclohexenylmalonato	ca. 40	$NaOC_2H_5$	Ethanol	150
	(Diethyl 2-cyclohexenylmalonate)	66	$NaOC_2H_5$	Ethanol	287, 150, 286, 706
1,2-Dibromocyclohexane	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	706
	Diethyl (2-hydroxycyclohexyl)malonato	—	$NaOC_2H_5$	Ethanol	706
Cyclohexene bromohydrin	Lactone from 2-hydroxycyclohexylacetic acid	>77	$NaOC_2H_5$	Ethanol	8, 707
Cyclohexene oxide	Lactone from diethyl (2-hydroxy-cyclohexyl)malonate	51	$NaOC_2H_5$	Ethanol	50, 708, 709
Cyclohexene oxide	Diethyl [β-(2-thienyl)ethyl]malonate	—	—	—	710
β-(2-Thienyl)ethyl chloride	None	—	$NaOC_2H_5$	Ethanol	710
4-Bromomethylpiperidine	Di-(1-nitroso-4-piperidylmethyl)malonic acid	79	$NaOC_2H_5$	Ethanol	710
1-Nitroso-4-bromo-methylpiperidine	Diethyl (2,4-dinitrophenyl)malonate	90	Na	Ether	139, 284
2,4-Dinitrochlorobenzene	Diethyl (2,4,6-trinitrophenyl)malonate	—	$NaOC_2H_5$	Ethanol	711
Picryl chloride	Diethyl (2,4-dinitrophenyl)malonato	—	$NaOC_2H_5$	Ethanol	184, 712
2,4-Dinitrobromobenzene	Diethyl (2,6-dinitro-4-chlorophenyl)malonate	22	Na	Ether	713, 714
2,5-Dichloro-1,3-dinitrobenzene	Diethyl (2,6-dinitro-4-bromophenyl)malonate	90	Na	Ether	715
1-Chloro-4-bromo-2,6-dinitrobenzene	Dimethyl (2,4-dinitro-3,5-dichlorophenyl)malonate*	—	Na	Ether	714
2,4-Dinitro-1,3,5-trichlorobenzene	Diethyl (2,4-dinitro-5-bromophenyl)malonate	40 (53)	$NaOC_2H_5$	Ethanol-C_6H_6	327, 326, 328
2,4-Dinitro-1,3,5-tribromobenzene					

Alkylating agent	Product	Yield (%)	Base	Solvent	References
n-C₃H₇OCH₂CH——CH₂ (epoxide)	n-C₃H₇OCH₂CHCH₂CHCO₂C₂H₅ (O—CO ring)	50–60	NaOC₂H₅	Ethanol	524
i-C₃H₇OCH₂CH——CH₂ (epoxide)	i-C₃H₇OCH₂CHCH₂CHCO₂C₂H₅ (O—CO ring)	50–60	NaOC₂H₅	Ethanol	524
i-C₃H₇C(CH₃)——CH₂ (epoxide)	i-C₃H₇C(CH₃)CH₂CHCO₂C₂H₅ (O—CO ring)	50–60	NaOC₂H₅	Ethanol	525
C₇					
n-C₇H₁₅Br	n-C₇H₁₅CH(CO₂C₂H₅)₂	82	NaOC₂H₅	Ethanol	656, 282
C₂H₅O(CH₂)₃Br	C₂H₅O(CH₂)₃CH(CO₂C₂H₅)₂	76	NaOC₂H₅	Ethanol	716
CH₃CO₂(CH₂)₃Cl-NaI	CH₂(CH₂)₄CHCO₂C₂H₅ (O—CO ring)	—	NaOC₂H₅	Ethanol	717
i-C₃H₇(CH₂)₄I	i-C₃H₇(CH₂)₄CH(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	138
i-C₅H₁₁CH(CH₃)I	i-C₅H₁₁CH(CH₃)CH(CO₂C₂H₅)₂	21	NaOC₂H₅	Ethanol	718
i-C₃H₇CH(CH₃)CH₂Br	i-C₃H₇CH(CH₃)CH₂CH(CO₂C₂H₅)₂	62	NaOC₂H₅	Ethanol	686
t-C₄H₉(CH₂)₃Br	t-C₄H₉(CH₂)₃CH(CO₂C₂H₅)₂	58	NaOC₂H₅	Ethanol	690
C₂H₅CH(CH₃)CH(CH₃)CH₂Br	C₂H₅CH(CH₃)CH(CH₃)CH₂CH(CO₂C₂H₅)₂	79	NaOC₂H₅	Ethanol	686
n-C₃H₇CH(CH₃)CH(CH₃)Br	n-C₃H₇CH(CH₃)CH(CH₃)CH(CO₂C₂H₅)₂	12	NaOC₂H₅	Ethanol	686
(C₂H₅)₂CBr(CH₂)₂Br	(C₂H₅)₂C=CHCH₂CHCH(CO₂C₂H₅)₂ and (C₄H₉O₂C)₂CHCH(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	697, 318, 667
n-C₄H₉CH(CH₂Br)₂	{ BrCH₂CH(C₄H₉-n)CH₂CH(CO₂C₂H₅)₂ Diethyl 3-n-butylcyclobutane-1,1-dicarboxylate	41 24	NaOC₂H₅	Ethanol	489
Chloropentamethylethane	(C₂H₅O₂C)₂CHCHCl(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	719
CH₂=CH(CH₂)₅Br	CH₂=CH(CH₂)₅CH(CO₂C₂H₅)₂	86	NaOC₂H₅	Ethanol	661
n-C₄H₉C≡CCH₂Br	n-C₄H₉C≡CCH₂CH(CO₂C₂H₅)₂	66	NaOC₂H₅	Ethanol	695
CH₃CHBr(CH₂)₂CO₂C₂H₅	C₂H₅O₂C(CH₂)₂C(CH₃)CH(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	720

Note: References 577–1080 are on pp. 322–331.
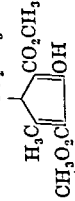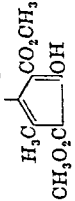
* Dimethyl malonato was used in this experiment.

TABLE I—*Continued*

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

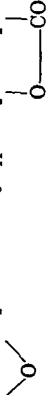| Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$Br(CH_2)_2CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_2CH(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	Ethanol-C_6H_6	668
$i\text{-}C_3H_7CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_3H_7\text{-}i)CH(CO_2C_2H_5)_2$	38	$NaOC_2H_5$	Ethanol	223
$C_2H_5OCH_2CHBrCO_2C_2H_5$	$C_2H_5OCH_2CHCO_2C_2H_5$ — $CH(CO_2C_2H_5)_2$	64	Na	—	721
$ClCH(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	>50	$NaOC_2H_5$	Ethanol	722
$BrCH(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	675
$CH_3COCHBrCH_2CO_2C_2H_2$	$CH_3COCHCH(CO_2C_2H_5)_2$ — $CH_2CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	723, 108
β-Cyclopentylethyl bromide	Diethyl (β-cyclopentylethyl)malonate	—	Na	Xylene	724
β-Cyclopentylethyl bromide	Diethyl (β-cyclopentylethyl)malonate	50–60	$NaOC_2H_5$	Ethanol	725
β-(2-Cyclopentenyl)ethyl bromide	Diethyl [β-(2-cyclopentenyl)ethyl]malonate	—	Na	Xylene	726
β-(2-Cyclopentenyl)ethyl bromide	Diethyl [β-(2-cyclopentenyl)ethyl]malonate	—	$NaOC_2H_5$	Ethanol	727
γ-Tetrahydrofurfurylpropyl bromide	Diethyl (γ-tetrahydrofurfurylpropyl)malonate	65–66	—	—	728
Bromomethylcyclohexane	Diethyl (cyclohexylmethyl)malonate	71	$NaOC_2H_5$	Ethanol	704
1-Methylcyclohexyl chloride	Diethyl (1-methylcyclohexyl)malonate	—	$NaOC_2H_5$	Ethanol	150
2-Methylcyclohexyl bromide	Diethyl (2-methylcyclohexyl)malonate	49	Na	—	147
3-Methylcyclohexyl bromide	Diethyl (3-methylcyclohexyl)malonate (cis and trans isomers)	Good	$NaOC_2H_5$	Ethanol	729
	Diethyl di-(3-methylcyclohexyl)malonate	—			

Reactant	Product	Yield %	Base	Solvent	References
3-Methylcyclohexyl iodide	Diethyl (3-methylcyclohexyl)malonate	40	$NaOC_2H_5$	Ethanol	352
4-Methylcyclohexyl bromide	Diethyl (4-methylcyclohexyl)malonate	—	$NaOC_2H_5$	Ethanol	149
4-Methylcyclohexyl iodide	Diethyl (4-methylcyclohexyl)malonate	55	$NaOC_2H_5$	Ethanol	352
1-Bromomethyl-1-bromocyclohexane	(cyclohexene ring)$CH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	150
1-Methyl-1,2-dibromocyclohexane	Diethyl (2-methyl-2-cyclohexenyl)malonate	—	$NaOC_2H_5$	Ethanol	150, 730
1-Methyl-1,2-dibromocyclohexane	Diethyl (5-methyl-2-cyclohexenyl)malonate (isomers)	—	—	—	730
(±)-5-Methyl-1,2-dibromocyclohexane	Two products, no analyses given	—	$NaOC_2H_5$	Ethanol	150
1-Cyano-1,2-dibromocyclohexane	Structure of product not determined	—	$NaOC_2H_5$	Ethanol	150
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(CO_2C_2H_5)_2$	80	NaH	$t\text{-}C_4H_9OH$	393
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(CO_2C_2H_5)_2$	24	KOH	$CH_3CH(OC_2H_5)_2$	83
$C_6H_5CH_2Cl$	$(C_6H_5CH_2CH(CO_2C_2H_5)_2$	85	$NaOC_2H_5$	Ethanol	136, 107, 108, 113, 119, 121, 142, 411, 430, 433, 571, 732, 734, 735
$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2C(CO_2C_2H_5)_2$	12			
$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2C(CO_2C_2H_5)_3$	84–87	$NaOC_2H_5$	Ethanol	733
$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2C(CO_2C_2H_5)_2$	—	$Mg(OC_2H_5)_2$	Ethanol	56
$o\text{-}ClC_6H_4CH_2Cl$	$o\text{-}ClC_6H_4CH_2CH(CO_2C_2H_5)_2$	76	$NaOC_2H_5$	Ethanol	736, 737
$o\text{-}ClC_6H_4CH_2Cl$	$(o\text{-}ClC_6H_4CH_2)_2C(CO_2C_2H_5)_2$	7			
$m\text{-}ClC_6H_4CH_2Cl$	$m\text{-}ClC_6H_4CH_2CH(CO_2C_2H_5)_2$	35	$NaOC_2H_5$	Ethanol	115
$m\text{-}ClC_6H_4CH_2Cl$	$(m\text{-}ClC_6H_4CH_2)C(CO_2C_2H_5)_2$	—			
$p\text{-}ClC_6H_4CH_2Cl$	$p\text{-}ClC_6H_4CH_2CH(CO_2C_2H_5)_2$	50	—	—	738
$p\text{-}ClC_6H_4CH_2Cl$	$(p\text{-}ClC_6H_4CH_2)_2C(CO_2C_2H_5)_2$	—			

Note: References 577–1080 are on pp. 322–331.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$o\text{-}BrC_6H_4CH_2Cl$	$o\text{-}BrC_6H_4CH_2CH(CO_2C_2H_5)_2$	Good	$NaOC_2H_5$	Ethanol	406
$o\text{-}BrC_6H_4CH_2Br$	$\{p\text{-}BrC_6H_4CH_2CH_2CH(CO_2C_2H_5)_2$ $(p\text{-}BrC_6H_4CH_2)_2C(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	738
$p\text{-}BrC_6H_4CH_2Br$	$p\text{-}IC_6H_4CH_2CH(CO_2C_2H_5)_2$	54	$NaOC_2H_5$	Ethanol	391
$p\text{-}IC_6H_4CH_2Br$	$(o\text{-}O_2NC_6H_4CH_2)_2C(CO_2CH_3)_2$*	—	$NaOCH_3$	CH_3OH	739
$o\text{-}O_2NC_6H_4CH_2CH_2Cl$	$\{o\text{-}O_2NC_6H_4CH_2CH_2CH(CO_2C_2H_5)_2$ $(o\text{-}O_2NC_6H_4CH_2)_2C(CO_2C_2H_5)_2$	54	$NaOC_2H_5$	Ethanol	112, 740, 741
$o\text{-}O_2NC_6H_4CH_2Cl$	$m\text{-}O_2NC_6H_4CH_2CH(CO_2CH_3)_2$* and $(m\text{-}O_2NC_6H_4CH_2)_2C(CO_2CH_3)_2$*	46	$NaOCH_3$	CH_3OH	342
$m\text{-}O_2NC_6H_4CH_2CH_2Cl$	$m\text{-}O_2NC_6H_4CH_2CH(CO_2H)_2$ and $(m\text{-}O_2NC_6H_4CH_2)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	117
$m\text{-}O_2NC_6H_4CH_2Cl$	$p\text{-}O_2NC_6H_4CH_2CH(CO_2CH_3)_2$*	—	$NaOCH_3$	CH_3OH	342
$p\text{-}O_2NC_6H_4CH_2X$**	$\{p\text{-}O_2NC_6H_4CH_2CH(CO_2C_2H_5)_2$ $(p\text{-}O_2NC_6H_4CH_2)_2C(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	118, 112, 740–742
$p\text{-}O_2NC_6H_4CH_2Cl$	$(p\text{-}O_2NC_6H_4CH_2)_2C(CO_2C_2H_5)_2$	18	Na	Ether	712
2-Nitro-4-cyanobromobenzene	Dimethyl (2-nitro-4-cyanophenyl)malonate*	—	$NaOC_2H_5$	Ethanol	98
o-Bromobenzoic acid	Diethyl (o-carboxyphenyl)malonate	50–60	$NaOC_2H_5$	Ethanol	524
$n\text{-}C_4H_9OCH_2CH{-}CH_2$ (epoxide O)	$n\text{-}C_4H_9OCH_2CHCH_2CHCO_2C_2H_5$ (O—CO ring, lactone)	50–60	$NaOC_2H_5$	Ethanol	525
$n\text{-}C_4H_9C(CH_3){-}CH_2$ (epoxide O)	$n\text{-}C_4H_9C(CH_3)CH_2CHCO_2C_2H_5$ (O—CO ring, lactone)				

Halide	Product	Yield %	Base	Solvent	References
$i\text{-}C_4H_9OCH_2CH\!\!-\!\!CH_2$ (epoxide, O)	$i\text{-}C_4H_9OCH_2CHCH_2CHCO_2C_2H_5$ (O—CO)	50–60	$NaOC_2H_5$	Ethanol	524
$i\text{-}C_4H_9C(CH_3)\!\!-\!\!CH_2$ (epoxide, O)	$i\text{-}C_4H_9C(CH_3)CH_2CHCO_2C_2H_5$ (O—CO)	50–60	$NaOC_2H_5$	Ethanol	525

C_8

Halide	Product	Yield %	Base	Solvent	References
$n\text{-}C_8H_{17}Br$	$n\text{-}C_8H_{17}CH(CO_2C_4H_9\text{-}t)_2$ ¶	71	NaH	$t\text{-}C_4H_9OH$	393
$n\text{-}C_8H_{17}Br$	$n\text{-}C_8H_{17}CH(CO_2C_2H_5)_2$	80–85	$NaOC_2H_5$	Ethanol	282, 743
$n\text{-}C_8H_{17}I$	$n\text{-}C_8H_{17}CH(CO_2C_2H_5)_2$	68	$NaOC_2H_5$	Ethanol	744
$n\text{-}C_8H_{17}I$	$(C_8H_{17}\text{-}n)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	745, 615
$n\text{-}C_6H_{13}CH(CH_3)Br$	$n\text{-}C_6H_{13}CH(CH_3)CH(CO_2C_2H_5)_2$	70–85	$NaOC_2H_5$	Ethanol	545, 746
$n\text{-}C_6H_{13}CH(CH_3)I$	$n\text{-}C_6H_{13}CH(CH_3)CH(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	399, 317
$n\text{-}C_5H_{11}CH(CH_3)CH_2I$	$n\text{-}C_5H_{11}CH(CH_3)CH_2CH(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	747
$i\text{-}C_3H_7(CH_2)_2I$	$i\text{-}C_3H_7(CH_2)_3CH(CO_2C_2H_5)_2$	73	$NaOC_2H_5$	Ethanol	138
$i\text{-}C_3H_7(CH_2)_2CH(CH_3)Br$	$i\text{-}C_3H_7(CH_2)_2CH(C_2H_5)CH(CO_2C_2H_5)_2$	43	$NaOC_2H_5$	Ethanol	718, 748
$n\text{-}C_4H_9CH(C_2H_5)CH_2Br$	$n\text{-}C_4H_9CH(C_2H_5)CH_2CH(CO_2C_2H_5)_2$	—	$NaOC_4H_9$	$n\text{-}C_4H_9OH$	749
$i\text{-}C_3H_7(CH_2)_3CH(CH_3)I$	$i\text{-}C_3H_7(CH_2)_3CH(CH_3)CH(CO_2C_2H_5)_2$	77	$NaOC_2H_5$	Ethanol	750
$i\text{-}C_3H_7CH_2COC(CH_3)_2Br$	$i\text{-}C_3H_7CH_2COC(CH_3)_2CH_2CO_2H$	—	$NaOC_2H_5$	Ethanol	751
$(C_2H_5)_2CBrCO_2C_2H_5$	$C_2H_5O_2CC(C_2H_5)_2CH(CO_2C_2H_5)_2$	—	Na	—	162
$CH_3CCl(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	752
$CH_3CBr(CO_2C_2H_5)_2$	$\{(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$ $CH_3C(CO_2C_2H_5)_2CH(CO_2C_2H_5)_2\}$	Low	$NaOC_2H_5$	Ethanol	752
$(+,-)\text{-}C_2H_5O_2CCHBr\text{-}CHBrCO_2C_2H_5$	$C_2H_5O_2CCH{-}C(CO_2C_2H_5)_2$ $CHCO_2C_2H_5$ Tetramethyl cyclopentane-1,2,2,3-tetracarboxylate*	80–90	$NaOC_2H_5$	Ethanol	175, 485
$CH_3O_2CCHBr(CH_2)_2\text{-}CHBrCO_2CH_3$ (low-melting isomer)		—	$NaOCH_3$	CH_3OH	753

Note: References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

** The halogen was not specified.

¶ Di-*t*-butyl malonate was used in this experiment.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$CH_3O_2CCHBr(CH_2)_2-$ $CHBrCO_2CH_3$ (high-melting isomer)	Tetramethyl cyclo-pentane-1,2,2,3-tetracarboxylate*	—	$NaOCH_3$	CH_3OH	753
$(CH_3O_2CCHBr)_2CHCH_3$	 CO_2CH_3 * CO_2CH_3 H_3C ─ OH CH_3O_2C or CO_2CH_3 * CO_2CH_3 H_3C ─ OH CH_3O_2C	68	$NaOCH_3$	CH_3OH	199, 200
γ-Cyclopentylpropyl bromide	Diethyl (γ-cyclopentylpropyl)malonate	83	$NaOC_2H_5$	Ethanol	751
β-Cyclohexylethyl bromide	Diethyl (β-cyclohexylethyl)malonate	50	$NaOC_2H_5$	Ethanol	704
β-Cyclohexylideneethyl bromide	Diethyl (β-cyclohexylideneethyl)malonate	50	$NaOC_2H_5$	Ethanol	603
β-(1-Cyclohexenyl)ethyl bromide	Diethyl [β-(1-cyclohexenyl)ethyl]malonate	58	K	C_6H_6	425
1-Bromo-1-ethylcyclohexane	Diethyl (1-ethylcyclohexyl)malonate	2	Na	Toluene	147
1-Ethyl-1,2-dibromocyclo-hexane	Diethyl (2-ethyl-2-cyclohexenyl)malonate	Poor	—	—	730
1,2-Dithiocyanocyclohexane	Diethyl 2-cyclohexenylmalonate	30	$NaOC_2H_5$	Ethanol	150, 322

$C_6H_5(CH_2)_2Cl$	$C_6H_5(HC_2)_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	427
$C_6H_5CH(CH_3)Br$	$[C_6H_5CH(CH_3)]_2C(CO_2C_2H_5)_2$	—	Na	Toluene	508
$C_6H_5(CH_2)_2Br$	$C_6H_5(CH_2)_2CH(CO_2C_2H_5)_2$	65	Na	Toluene	411
$C_6H_5(CH_2)_2Br$	$C_6H_5(CH_2)_2CH(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	755, 142, 428, 539, 756, 757
$C_6H_5O(CH_2)_2Br$	$C_6H_5O(CH_2)_2CH(CO_2C_2H_5)_2$	89	$NaOC_2H_5$	Ethanol	136, 758
$C_6H_5O(CH_2)_2Br$	$[C_6H_5O(CH_2)_2]_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	758
β-Phenoxyethyl p-toluenesulfonate	$C_6H_5O(CH_2)_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	335
$o\text{-}CH_3C_6H_4CH_2Cl$	$o\text{-}CH_3C_6H_4CH_2CH(CO_2H)_2$	60–70	$NaOC_2H_5$	Ethanol	759, 760
Chloromethyl-p-bromotoluene (mixture)	Diethyl [2(and 3)-bromo-5(and 6)-methylbenzyl]malonate	88	$NaOC_2H_5$	Ethanol	114
$o\text{-}CH_3C_6H_4CH_2Br$	$o\text{-}CH_3C_6H_4CH_2CH(CO_2H)_2$	—	$NaOC_2H_5$	Ethanol	761
$o\text{-}CH_3C_6H_4CH_2Br$	$o\text{-}CH_3C_6H_4CH_2CH(CO_2C_2H_5)_2$	57	Na	Benzene	421
$m\text{-}CH_3C_6H_4CH_2Br$	$m\text{-}CH_3C_6H_4CH_2CH(CO_2C_2H_5)_2$	66	$NaOC_2H_5$	Ethanol	133, 110, 762
$p\text{-}CH_3C_6H_4CH_2Cl$	$p\text{-}CH_3C_6H_4CH_2CH(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Toluene	507
2-Methoxy-5-nitrobenzyl chloride	Diethyl (2-methoxy-5-nitrobenzyl)malonate	—	—	—	763
$m\text{-}CH_3OC_6H_4CH_2Br$	$[m\text{-}CH_3OC_6H_4CH_2]_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	764
$p\text{-}CH_3OC_6H_4CH_2Cl$	$p\text{-}CH_3OC_6H_4CH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	511
$o\text{-}NCC_6H_4CH_2Cl$	$\{o\text{-}NCC_6H_4CH_2CH(CO_2C_2H_5)_2$ / $(o\text{-}NCC_6H_4CH_2)_2C(CO_2C_2H_5)_2\}$	Good	$NaOC_2H_5$	Ethanol	198, 109
$C_6H_5COCH_2Br$	$C_6H_5COCH_2CH(CO_2H)_2$	—	$NaOC_2H_5$	Ethanol	765, 106, 766
3-Nitro-4-bromoacetophenone	Dimethyl (2-nitro-4-acetylphenyl)malonate*	70	Na	Ether	712
3-Nitro-4-methyl-6-bromobenzonitrile	Dimethyl (2-cyano-4-nitro-5-methylphenyl)malonate*	Poor	Na	Ether	712
o-Xylylene dibromide	Diethyl hydrindene-2,2-dicarboxylate	75	$NaOC_2H_5$	Ethanol	767, 302, 486
$i\text{-}C_5H_{11}OCH_2CH\!-\!CH_2$ (epoxide O)	$i\text{-}C_5H_{11}OCH_2CHCH_2CHCO_2C_2H_5$, O——CO	50–60	$NaOC_2H_5$	Ethanol	524

Note: References 577–1080 are on pp. 322–331.

* Dimethyl malonate was used in this experiment.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, CH₂(CO₂R)₂

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
i-C₅H₁₁C(CH₃)—CH₂ (O)	i-C₅H₁₁C(CH₃)CH₂CH₂CHCO₂C₂H₅ | O—CO	50–60	NaOC₂H₅	Ethanol	525
C₆H₅CH—CH₂ (O)	C₆H₅CHCH₂CH₂ | CO | O—CO	76	NaOC₂H₅	Ethanol	526, 11
p-O₂NC₆H₄CH—CH₂ (O)	p-O₂NC₆H₄CHCH₂CHCO₂C₂H₅ | O—CO	46	NaOC₂H₅	Ethanol	12
C₉					
n-C₆H₁₃Br	n-C₆H₁₃CH(CO₂C₂H₅)₂	80–85	NaOC₂H₅	Ethanol	282
n-C₇H₁₅CH(CH₃)I	n-C₇H₁₅CH(CH₃)CH(CO₂C₂H₅)₂	90	NaOC₂H₅	Ethanol	317
n-C₅H₁₁CH(CH₃)(CH₂)₂Br	n-C₅H₁₁CH(CH₃)(CH₂)₂CH(CO₂C₂H₅)₂	78	NaOC₂H₅	Ethanol	317
i-C₃H₇(CH₂)₆I	i-C₃H₇(CH₂)₆CH(CO₂C₂H₅)₂	65	NaOC₂H₅	Ethanol	138
i-C₃H₇(CH₂)₄CH(CH₃)Br	i-C₃H₇(CH₂)₄CH(CH₃)CH(CO₂C₂H₅)₂	80	NaOC₂H₅	Ethanol	686
n-C₃H₇CH(CH₃)CH-(C₂H₅)CH₂Br	n-C₃H₇CH(CH₃)CH(C₂H₅)CH₂CH(CO₂C₂H₅)₂	63	NaOC₂H₅	Ethanol	686
CH₂=CH(CH₂)₃Br	CH₂=CH(CH₂)₃CH(CO₂C₂H₅)₂	81	NaOC₂H₅	Ethanol	601
C₂H₅CH=CH(CH₂)₂-CH=CHCH₂Cl	C₂H₅CH=CH(CH₂)₂CH=CH-CH₂CH(CO₂C₂H₅)₂	50	—	—	693
C₂H₅CH=C(CH₃)(CH₂)₄Br	C₂H₅CH=C(CH₃)(CH₂)₄CH(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	317
Br(CH₂)₆CO₂C₂H₅·NaI	C₂H₅O₂C(CH₂)₆CH(CO₂C₂H₅)₂	83	NaOC₂H₅	Ethanol	717
C₂H₄O₂CCHBrCH₂CHBr-CO₂C₂H₅	Tetraethyl cyclobutane-1,2,3,-tetracarboxylate	50	NaOC₂H₅	Ethanol	176
δ-Cyclopentylbutyl bromide	Diethyl (δ-cyclopentylbutyl)malonate	40	NaOC₂H₅	Ethanol	725
δ-Cyclopentylbutyl bromide	Diethyl (δ-cyclopentylbutyl)malonate	—	Na	Toluene	724

			Na	Toluene	....±
δ-(2-Cyclopentonyl)butyl bromide	Diethyl [δ-(2-cyclopentonyl)butyl]malonato	....	....	....	....
γ-Cyclohexylpropyl bromide	Diethyl [γ-cyclohexylpropyl]malonato	53	$NaOC_2H_5$	Ethanol	704
β-(2-Methyl-1-cyclohexenyl)-ethyl bromide	Diethyl [β-(2-methyl-1-cyclohexenyl)ethyl]malonato	71	K	C_6H_6	424
$C_6H_5(CH_2)_3Br$	$C_6H_5(CH_2)_3CH(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Ethanol	708, 429, 769, 770
$C_6H_5(CH_2)_3I$	$C_6H_5(CH_2)_3CH(CO_2C_2H_5)_2$	—	—	—	771
$C_6H_5CH_2O(CH_2)_2Cl$	$[C_6H_5CH_2O(CH_2)_2]_2C(CO_2C_2H_5)_2$	—	—	—	606
$C_6H_5O(CH_2)_3Cl$	$C_6H_5O(CH_2)_3CH(CO_2C_2H_5)_2$	56	$NaOC_2H_5$	Ethanol	772–774
$C_6H_5O(CH_2)_3Br$	$C_6H_5O(CH_2)_3CH(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	Ethanol	775, 698, 776, 777
$C_6H_5CH_2CH_2CH(CH_3)Br\cdot KI$	$C_6H_5CH_2CH_2CH(CH_3)CH(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	432
$C_6H_5CH=CHCH_2Cl$	$C_6H_5CH=CHCH_2CH(CO_2C_2H_5)_2$	51	$NaOC_2H_5$	Ethanol	18
$m\text{-}CH_3C_6H_4(CH_2)_2Br$	$m\text{-}CH_3C_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$	85	$NaOC_2H_5$	Ethanol	517
$p\text{-}CH_3C_6H_4(CH_2)_2Br$	$p\text{-}CH_3C_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$	Good	K	Toluene	760
$m\text{-}CH_3OC_6H_4(CH_2)_2Br$	$m\text{-}CH_3OC_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$	82–85	K	Toluene	412
2-Bromo-5-ethylbenzyl chloride	Diethyl (2-bromo-5-ethylbenzyl)malonato	78	$NaOC_2H_5$	Ethanol	407
2,4-Dimethylbenzyl chloride	Diethyl (2,4-dimethylbenzyl)malonato	49	Na	Xylene	778, 760
3,5-Dimethylbenzyl bromide	Diethyl (3,5-dimethylbenzyl)malonato	30	$NaOC_2H_5$	Ethanol	779, 738
2-Methyl-5-methoxybenzyl chloride	Diethyl (2-methyl-5-methoxybenzyl)malonato	77	$NaOC_2H_5$	Ethanol	404
2-Chloro-5-nitro-4-methylacetophenone	Diethyl (2-acetyl-4-nitro-5-methyl-phenyl)malonato	—	Na	Ether	712
Methyl p-chloromethylbenzoate	Diethyl (p-carbomethoxybenzyl)malonato	66	$NaOC_2H_5$	Ethanol	780
$C_6H_5CH_2COCH_2Cl$	$(C_6H_5CH_2COCH_2)_2C(CO_2C_2H_5)_2$	—	$Mg(OC_2H_5)_2$	Ethanol	56
2,3-Dichloroindenone	Diethyl (2-chloro-3-indenonyl)malonato	—	$NaOC_2H_5$	Ethanol	781
$n\text{-}C_9H_{19}OCH_2CH\!\!-\!\!CH_2$ (epoxide)	$n\text{-}C_9H_{19}OCH_2CHCH_2CHCH_2CHCO_2C_2H_5$ ($O\!-\!\!-\!\!CO$)	50–60	$NaOC_2H_5$	Ethanol	524

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$n\text{-}C_6H_{13}C(CH_3)$—$CH_2$ $\diagdown$ O $\diagup$	$n\text{-}C_6H_{13}C(CH_3)CH_2CH_2CHCO_2C_2H_5$ O—CO	50–60	$NaOC_2H_5$	Ethanol	525
$C_6H_5OCH_2CH$—CH_2 $\diagdown$ O $\diagup$	$C_6H_5OCH_2CHCH_2CHCO_2C_2H_5$ O—CO	50–60	$NaOC_2H_5$	Ethanol	524
$C_6H_5C(CH_3)$—CH_2 $\diagdown$ O $\diagup$	$C_6H_5C(CH_3)CH_2CH_2CHCO_2C_2H_5$ O—CO	50–60	$NaOC_2H_5$	Ethanol	525
3-Chloromethylthianaphtheno	Diethyl (3-thianaphthenemethyl)malonate	45	Na	C_6H_6	782
C_{10}					
$n\text{-}C_{10}H_{21}Br\text{-}KI$	$n\text{-}C_{10}H_{21}CH(CO_2C_2H_5)_2$	85	$NaOC_2H_5$	Ethanol	70, 282, 289
$n\text{-}C_{10}H_{21}I$	$n\text{-}C_{10}H_{21}CH(CO_2C_2H_5)_2$	93	$NaOC_2H_5$	Ethanol	684
$n\text{-}C_8H_{17}CH(CH_3)Br$	$n\text{-}C_8H_{17}CH(CH_3)CH(CO_2C_4H_9)_2\dagger\dagger$	82	—	—	784
$n\text{-}C_5H_{11}CH(C_4H_9\text{-}n)I$	$n\text{-}C_5H_{11}CH(C_4H_9\text{-}n)CH(CO_2C_2H_5)_2$	65	$NaOC_2H_5$	Ethanol	141
$i\text{-}C_3H_7(CH_2)_3CH(CH_3)\text{-}$ $(CH_2)_2Br$	$i\text{-}C_3H_7(CH_2)_3CH(CH_3)(CH_2)_2CH(CO_2C_2H_5)_2$	50	—	—	743
Geranyl chloride	Diethyl geranylmalonate	43	$NaOC_2H_5$	Ethanol	18, 282, 785
Geranyl bromide	Diethyl geranylmalonate	52	$NaOC_2H_5$	Ethanol	19
Linalyl bromide	Diethyl geranylmalonate	52	$NaOC_2H_5$	Ethanol	19
$i\text{-}C_3H_7(CH_2)_3CH(CH_3)\text{-}$ $COCH_2Br$	$i\text{-}C_3H_7(CH_2)_3CH(CH_3)COCH_2CH(CO_2C_2H_5)_2$	84	Na	C_6H_6	786
$C_2H_5O_2C(CH_2)_8CHBrCO_2C_2H_5$	$C_2H_5O_2C(CH_2)_8CH(CO_2C_2H_5)CH(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	787
$C_2H_5O_2C(CH_2)_8CHBrCO_2C_2H_5$	$[C_2H_5O_2C(CH_2)_8CH(CO_2C_2H_5)]_2C(CO_2C_2H_5)_2$	10	$NaOC_2H_5$	Ethanol	787
$Br(CH_2)_{10}Br$	$Br(CH_2)_{10}CH(CO_2C_2H_5)_2$	33	$NaOC_2H_5$	Ethanol	788

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$
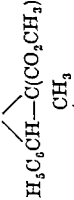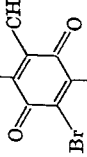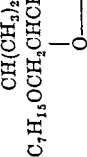
(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
3-Bromomethylindene	Diethyl (3-indenylmethyl)malonate $CHCO_2CH_3$* $CHCO_2CH_3$	79	$NaOC_2H_5$	Ethanol	799
$C_6H_5CHBrCHBrCO_2CH_3$	$H_5C_6CH—C(CO_2CH_3)_2$ CH_3	—	$NaOCH_3$	CH_3OH	800
Dibromothymoquinone	$CH(CO_2C_2H_5)_2$ (quinone structure) $CH(CH_3)_2$ Br	—	$NaOC_2H_5$	Ethanol	801
$n\text{-}C_7H_{15}OCH_2CH—CH_2$ $\diagdown O$	$n\text{-}C_7H_{15}OCH_2CHCH_2CHCO_2C_2H_5$ —O——CO	50–60	$NaOC_2H_5$	Ethanol	524
$C_6H_5CH_2OCH_2CH—CH_2$ $\diagdown O$	$C_6H_5CH_2OCH_2CHCH_2CHCO_2C_2H_5$ —O——CO	50–60	$NaOC_2H_5$	Ethanol	524
$o\text{-}CH_3C_6H_4OCH_2CH—CH_2$ $\diagdown O$	$o\text{-}CH_3C_6H_4OCH_2CHCH_2CHCO_2C_2H_5$ —O——CO	50–60	$NaOC_2H_5$	Ethanol	524
$o\text{-}CH_3OC_6H_4OCH_2CH—CH_2$ $\diagdown O$	$o\text{-}CH_3OC_6H_4OCH_2CHCH_2CHCO_2C_2H_5$ —O——CO	50–60	$NaOC_2H_5$	Ethanol	524
$m\text{-}CH_3C_6H_4OCH_2CH—CH_2$ $\diagdown O$	$m\text{-}CH_3C_6H_4OCH_2CHCH_2CHCO_2C_2H_5$ —O——CO	50–60	$NaOC_2H_5$	Ethanol	524

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
3,4-Dibromo-β-naphthoquinone	Diethyl [(?)-bromo-β-naphthoquinone]malonate	—	$NaOC_2H_5$	Ethanol	781
C_{11}					
n-$C_{11}H_{23}Br$	n-$C_{11}H_{23}CH(CO_2C_2H_5)_2$	80–85	$NaOC_2H_5$	Ethanol	282, 802
n-$C_9H_{19}CH(CH_3)Br$-NaI	n-$C_9H_{19}CH(CH_3)CH(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	70
$CH_2=CH(CH_2)_9Cl$-KI	$CH_2=CH(CH_2)_9CH(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	804
n-$C_4H_9CH(C_2H_5)$-$(CH_2)CH(CH_3)Br$	n-$C_4H_9CH(C_2H_5)(CH_2)_2CH(CH_3)$-$CH(CO_2C_2H_5)_2$	71	$NaOC_2H_5$	Ethanol	686
ε-Cyclohexylpentyl bromide	Diethyl (ε-cyclohexylpentyl)malonate	79	$NaOC_2H_5$	Ethanol	704
$C_6H_5O(CH_2)_5Br$	$C_6H_5O(CH_2)_5CH(CO_2C_2H_5)_2$	53	$NaOC_2H_5$	Ethanol	803
n-$C_4H_9CH(C_6H_5)Cl$	n-$C_4H_9CH(C_6H_5)CH(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	805
t-$C_4H_9CH(C_6H_5)Br$	t-$C_4H_9CH(C_6H_5)CH(CO_2C_2H_5)_2$	24	$NaOC_2H_5$	Ethanol	806
p-t-$C_4H_9C_6H_4CH_2Cl$	p-t-$C_4H_9C_6H_4CH_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	403
γ-(2-Methyl-5-methoxyphenyl)propyl bromide	Diethyl [γ-(2-methyl-5-methoxyphenyl)propyl]malonate	49	$NaOC_2H_5$	Ethanol	404
β-(2,5-Dimethyl-4-methoxyphenyl)ethyl bromide	Diethyl [β-(2,5-dimethyl-4-methoxyphenyl)ethyl]malonate	54	$NaOC_2H_5$	Ethanol	807
2-Methyl-5-isopropylbenzyl chloride	Diethyl (2-methyl-5-isopropylbenzyl)malonate	60	Na	C_6H_6	808, 418, 779
2,3,5,6-Tetramethylbenzyl chloride	Diethyl (2,3,5,6-tetramethylbenzyl)malonate	66	Na	C_6H_6	809
2,3,5,6-Tetramethylbenzyl chloride	β-(2,3,5,6-Tetramethylphenyl)propionic acid	72	$NaOC_2H_5$	Ethanol	810

	Yield / Temp	Base	Solvent	Reference
ω-Chloro-2,5-dimethyl-propiophenone — Diethyl [β-(2,5-dimethylbenzoyl)ethyl]-malonate	—	NaOC$_2$H$_5$	Ethanol	779
n-C$_8$H$_{17}$OCH$_2$CH—CH$_2$ (O) — n-C$_8$H$_{17}$OCH$_2$CHCH$_2$CHCO$_2$C$_2$H$_5$	50–60	NaOC$_2$H$_5$	Ethanol	524
C$_6$H$_5$(CH$_2$)$_2$OCH$_2$CH—CH$_2$ (O) — C$_6$H$_5$(CH$_2$)$_2$OCH$_2$CHCH$_2$CHCO$_2$C$_2$H$_5$	50–60	NaOC$_2$H$_5$	Ethanol	524
γ-Bromopropylphthalimide — Diethyl (γ-phthalimidopropyl)malonate	—	NaOC$_2$H$_5$	Ethanol	811
4-Chloromethyl-2-(4-methoxyphenyl)thiazole — Diethyl [2-(4-methoxyphenyl)-4-thiazolemethyl]malonate	52	—	—	140
C$_6$H$_5$CHBr(CH$_2$)$_4$Br — Diethyl 2-phenylcyclohexane-1,1-dicarboxylate (CHCO$_2$C$_2$H$_5$)	—	NaOC$_2$H$_5$	Ethanol	812
C$_6$H$_5$CHBrCHBrCO$_2$C$_2$H$_5$ — H$_5$C$_6$CH—C(CO$_2$C$_2$H$_5$)$_2$	—	NaOC$_2$H$_5$	Ethanol	813
C$_6$H$_5$C=CCO$_2$C$_2$H$_5$ (Br Br) — C$_2$H$_5$O$_2$CCH=C(C$_6$H$_5$)CBr(CO$_2$C$_2$H$_5$)$_2$	—	Na	Ether	813
C$_6$H$_5$C=CCO$_2$C$_2$H$_5$ (Br Br) — (C$_2$H$_5$O$_2$C)$_2$CHCH(CO$_2$C$_2$H$_5$)$_2$	—	NaOC$_2$H$_5$	Ethanol	813
NCH$_2$CH—CH$_2$ (phthalimide, O) — α-Carbethoxy-δ-phthalimido-γ-valerolactone	60	NaOC$_2$H$_5$	Ethanol	464
2-Chloromethyl-5,6,7,8-tetrahydronaphthalene — CH$_2$CH(CO$_2$C$_2$H$_5$)$_2$	—	—	—	513
1-Chloromethylnaphthalene — Diethyl (1-naphthylmethyl)malonate	82	NaOC$_2$H$_5$	Ethanol	409, 512, 738

Note: References 577–1080 are on pp. 322–331.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
ethylnaphthalene bromomethyl- bene	Diethyl (1-naphthylmethyl)malonate	55	Na	C_6H_6	153
	Diethyl (4-bromo-1-naphthylmethyl)malonate	—	Na	C_6H_6	153
ethylnaphthalene bromomethyl- bene	Diethyl (2-naphthylmethyl)malonate	—	Na	C_6H_6	153
	Diethyl (1-bromo-2-naphthylmethyl)malonate	—	Na	C_6H_6	153
$(CH_3)_2CH\cdot$ I_2Br $)(CO_2C_2H_5)_2$	$(n\text{-}C_{12}H_{13})_2C(CO_2H)_2$	61	$NaOC_2H_5$	Ethanol	684
	$n\text{-}C_6H_{13}CH(CH_3)CH(C_2H_5)CH_2CH_2CH(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	686
	$(C_2H_5O_2C)_2C(C_2H_5)(CH_2)_3CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	814, 656
$_4H_3$ $_2(CH_2)_4Br$ $_2)_4Br$	$cyclo\text{-}C_6H_{11}(CH_2)_4CH(CO_2C_2H_5)_2$	63	$NaOC_2H_5$	Ethanol	704
	$C_6H_5O(CH_2)_6CH(CO_2C_2H_5)_2$	71	$NaOC_2H_5$	Ethanol	815, 816
$H_4(CH_2)_2Br$	$[p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2CH(CO_2C_2H_5)_2$	50	Na	C_6H_6	321
	$[p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2]_2C(CO_2C_2H_5)_2$	—			
hyl-1-isopropyl- lbenzene	$\overset{CH_3}{\underset{CH(CH_3)_2}{\bigodot}}(CH_2)_2CH(CO_2C_2H_5)_2$	30	Na	C_6H_6	415
.l-2-methyl-4- ybenzyl chloride	Diethyl (2-methyl-4-methoxy-5- isopropylbenzyl)malonate	63	$NaOC_2H_5$	Ethanol	404
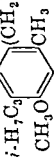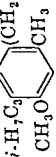
TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
β-(2-Methyl-4-t-butylphenyl)-ethyl bromide	Diethyl [β-(2-methyl-4-t-butylphenyl)ethyl]-malonate	80	$NaOC_2H_5$	Ethanol	827, 414
β-(2-Methoxy-5-t-butylphenyl)ethyl bromide	Diethyl [β-(2-methoxy-5-t-butyl-phenyl)ethyl]malonate	52	$NaOC_2H_5$	Ethanol	827
2,4-Dimethyl-5-t-butylbenzyl chloride	Diethyl (2,4-dimethyl-5-t-butylbenzyl)malonate	19	$NaOC_2H_5$	Ethanol	405
$i\text{-}H_7C_3$—[ring, CH_3O, CH_3]—$(CH_2)_2Br$	Diethyl $i\text{-}H_7C_3$—[ring, CH_3O, CH_3]—$(CH_2)_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	321
$i\text{-}H_7C_3$—[ring, CH_3O, CH_3]—$(CH_2)_2Br$	$i\text{-}H_7C_3$—[ring, CH_3O, CH_3]—$(CH_2)_2CH(CO_2C_2H_5)_2$	61	Na	Toluene	413
1-Benzoyl-4-bromo-methylpiperidine	Diethyl [(1-benzoyl-4-piperidyl)-methyl]malonate	—	$NaOC_2H_5$	Ethanol	828
Benzhydryl bromide	Diethyl benzhydrylmalonate	49	$NaOC_2H_5$	Ethanol	516, 829
$o\text{-}C_6H_5C_6H_4CH_2Br$	$o\text{-}C_6H_5C_6H_4CH_2CH(CO_2C_2H_5)_2$	80	—	—	830
$p\text{-}C_6H_5C_6H_4CH_2CH_2Cl$	$p\text{-}C_6H_5C_6H_4CH_2CH_2CH(CO_2C_2H_5)_2$ and $(p\text{-}C_6H_5C_6H_4CH_2CH_2)_2C(CO_2C_2H_5)_2$	65	—	—	738
3-Nitro-4-bromobenzophenone	Diethyl (2-nitro-4-benzoylphenyl)malonate	—	Na	Ether	712
β-(5-Methoxy-1-naphthyl)-ethyl bromide	Diethyl [β-(5-methoxy-1-naphthyl)ethyl]-malonate	65	$NaOC_2H_5$	Ethanol	520
β-(7-Methoxy-2-naphthyl)-ethyl bromide	Diethyl [β-(7-methoxy-2-naphthyl)ethyl]-malonate	80	Na	C_6H_6	819
β-(6-Methoxy-1-naphthyl)-ethyl bromide	Diethyl [β-(6-methoxy-1-naphthyl)ethyl]-malonate	37	K	Toluene	831
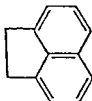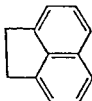
Halide	Product	Yield (%)	Condensing agent	Solvent	Reference
![C(CH₃)₂Cl tetralin] $C(CH_3)_2Cl$	$C(CH_3)_2CH(CO_2H)_2$	15	Na	Ether	832
1-Chloromethyl-2-ethyl-naphthalene	Diethyl (2-ethyl-1-naphthylmethyl)malonate	—	—	—	821
1-Chloromethyl-2,3-dimethylnaphthalene	Diethyl (2,3-dimethyl-1-naphthylmethyl)-malonate	—	—	—	821
1-Chloromethyl-3,4-dimethyhnaphthalene	Diethyl (3,4-dimethyl-1-naphthylmethyl)-malonate	—	—	—	921
9-Bromofluorene	Fluorenyl-9-acetic acid	89	$NaOC_2H_5$	Ethanol	833, 516
C_{11}–C_{18}					
$n\text{-}C_{11}H_{23}I$	$n\text{-}C_{11}H_{23}CH(CO_2C_2H_5)_2$	96	Na	None	684
$n\text{-}C_4H_9CH(C_2H_5)(CH_2)_2Br$	$n\text{-}C_4H_9CH(C_2H_5)(CH_2)_2CH(C_4H_9\text{-}i)\text{-}CH(CO_2C_2H_5)_2$	31	$NaOC_2H_5$	Ethanol	686
$n\text{-}C_4H_9CH(C_6H_5)(CH_2)_3Br$	$n\text{-}C_4H_9CH(C_6H_5)(CH_2)_3CH(CO_2C_2H_5)_2$	66	$NaOC_2H_5$	Ethanol	805
$p\text{-}C_6H_5COC_6H_4CH_2CH_2Br$	$(p\text{-}C_6H_5COC_6H_4CH_2CH_2)_2C(CO_2C_2H_5)_2$	76	$NaOC_2H_5$	C_6H_6	834
![biphenyl bis(CH₂Br)] CH_2Br / CH_2Br	![biphenyl C(CO₂C₂H₅)₂] $C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	492
$t\text{-}H_9C_4$···$(CH_2)_2Br$ / CH_3O···CH_3	$t\text{-}H_9C_4$···$(CH_2)_2CH(CO_2C_2H_5)_2$ / CH_3O···CH_3	—	—	—	414
$p\text{-}CH_3OC_6H_4SO_2C_6H_4CH_2Br\text{-}p$	$p\text{-}CH_3OC_6H_4SO_2C_6H_4CH_2CH(CO_2C_2H_5)_2$	40	Na	C_6H_6	245
1-Chloromethyl-4-isopropylnaphthalene	Diethyl (4-isopropyl-1-naphthylmethyl)malonate	—	$NaOC_2H_5$	Ethanol	515

Note: References 577–1080 are on pp. 322–331.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$(CH_2)_2Br$	$(CH_2)_2CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	835
$Br(CH_2)_3C(C_7H_{15}-n)(CO_2CH_3)_2$	$(CH_3O_2C)_2C(C_7H_{15}-n)(CH_2)_3CH(CO_2CH_3)_2$*	—	Na	None	656
3,7,11-Trimethyl-2-dodecenyl bromide	Diethyl (3,7,11-trimethyl-2-dodecenyl)-malonate	—	$NaOC_2H_5$	Ethanol	836
Farnesyl bromide	Diethyl farnesylmalonate	56	$NaOC_2H_5$	Ethanol	837
$Br(CH_2)_3C(C_5H_{11}-n)(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2C(C_5H_{11}-n)(CH_2)_3CH(CO_2C_2H_5)_2$	—	—	—	656
$(C_2H_5O_2C)_2CBrCH_2CBr(CO_2C_2H_5)_2$	$C(CO_2C_2H_5)_2$ $CH_2—C(CO_2C_2H_5)_2$ and $(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	261
n-$C_5H_{11}CH(C_6H_5)Cl$	n-$C_5H_{11}CH(C_6H_5)CH(CO_2C_2H_5)_2$	56	$NaOC_2H_5$	Ethanol	805
1-Chloromethyl-2-t-butylnaphthalene	Diethyl (2-t-butyl-1-naphthyl-methyl)malonato	—	—	—	821
β-(5-Isopropyl-1-naphthyl)-ethyl bromide	Diethyl [β-(5-isopropyl-1-naphthyl)ethyl]-malonato	59	$NaOCH_3$	Xylene	938

Halide	Product	Yield (%)	Base	Solvent	References
[fused tricyclic ketone structure drawn] CH_3Br	$CH_3CH_2CO_2H$	24	Na	C_6H_6-ethanol	839
$n\text{-}C_{16}H_{33}Br$	$n\text{-}C_{16}H_{33}CH(CO_2C_2H_5)_2$	94	$NaOC_2H_5$	Ethanol	679, 840, 841
$n\text{-}C_{16}H_{33}I$	$n\text{-}C_{16}H_{33}CH(CO_2C_2H_5)_2$ and $(n\text{-}C_{16}H_{33})_2C(CO_2C_2H_5)_2$	40	$NaOC_2H_5$	Ethanol	842
$n\text{-}C_6H_{13}CH{=}CH(CH_2)_8Br$	$n\text{-}C_6H_{13}CH{=}CH(CH_2)_8CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	843
$C_2H_5CH{=}CH(CH_2)_{12}Br$	$C_2H_5CH{=}CH(CH_2)_{12}CH(CO_2C_2H_5)_2$	40–50	$NaOC_4H_9\text{-}n$	$n\text{-}C_4H_9OH$	844
$n\text{-}C_5H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_6I$	$n\text{-}C_5H_{11}C{\equiv}CCH_2C{\equiv}C(CH_2)_6CH(CO_2C_2H_5)_2$	>29	$NaOC_2H_5$	Ethanol	845, 846
Hydnocarpyl bromide	Diethyl hydnocarpylmalonate	59	$NaOC_2H_5$	Ethanol	847
$(C_2H_5O_2C)_2CBr(CH_2)_2{\cdot}CBr(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$ and $\begin{array}{l}CH_2{-}C(CO_2C_2H_5)_2\\CH_2{-}C(CO_2C_2H_5)_2\end{array}$	—	$NaOC_2H_5$	Ethanol	261
[fused tricyclic ketone structure drawn] CH_3Br					
$n\text{-}C_9H_{19}CH(C_6H_5)Cl$	$n\text{-}C_9H_{19}CH(C_6H_5)CH(CO_2C_2H_5)_2$	61	$NaOC_2H_5$	Ethanol	805
$n\text{-}C_4H_9CH(C_6H_5)(CH_2)_3Br$	$n\text{-}C_4H_9CH(C_6H_5)(CH_2)_3CH(CO_2C_2H_5)_2$	67	$NaOC_2H_5$	Ethanol	805
$n\text{-}C_{17}H_{35}I$	$n\text{-}C_{17}H_{35}CH(CO_2C_2H_5)_2$	92	Na	C_6H_6	400
$n\text{-}C_{15}H_{31}CH(CH_3)Br$	$n\text{-}C_{15}H_{31}CH(CH_3)CH(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	281
$n\text{-}C_{15}H_{31}CH(CH_3)I$	$n\text{-}C_{15}H_{31}CH(CH_3)CH(CO_2C_2H_5)_2$	90	$NaOC_2H_5$	Ethanol	281
3-Chloromethylpyrene	Diethyl (3-pyrenylmethyl)malonate	76	Na	C_6H_6	848
$n\text{-}C_{18}H_{37}I$	$n\text{-}C_{18}H_{37}CH(CO_2C_2H_5)_2$	100	$NaOC_4H_9\text{-}n$	$n\text{-}C_4H_9OH$	46, 45, 684
Oleyl bromide	Diethyl oleylmalonate	53	—	—	849
Oleyl tosylate	Diethyl oleylmalonate	60	—	—	849
Chaulmoogryl bromide	Diethyl chaulmoogrylmalonate	—	$NaOC_2H_5$	Ethanol	850
$n\text{-}C_4H_9CH(C_6H_5)(CH_2)_7Cl$	$n\text{-}C_4H_9CH(C_6H_5)(CH_2)_7CH(CO_2C_2H_5)_2$	61	$NaOC_2H_5$	Ethanol	805
$3\text{-}(\alpha\text{-Bromoethyl})pyrene$	Diethyl [α-(3-pyrenyl)ethyl]malonate	>93	Na	C_6H_6	848

Note: References 577–1080 are on pp. 322–331.
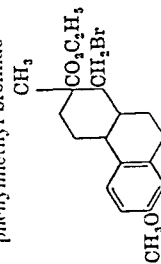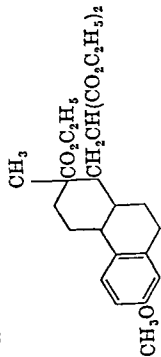
* Dimethyl malonate was used in this experiment.

TABLE I—Continued

ALKYLATION OF MALONIC ESTERS, $CH_2(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_{16}–C_{24}					
n-$C_5H_{11}CH(C_6H_5)(CH_2)_3Br$	n-$C_5H_{11}CH(C_6H_5)(CH_2)_3CH(CO_2C_2H_5)_2$	72	$NaOC_2H_5$	Ethanol	805
Dinesitylchloromethane	Diethyl (dimesitylmethyl)malonate	84	$Mg(OC_2H_5)_2$	Ether-ethanol	218
$(C_6H_5)_3CCl$	$(C_6H_5)_3CCH(CO_2C_2H_5)_2$	86	$Mg(OC_2H_5)_2$	Ether	56
$(C_6H_5)_3CBr$	$(C_6H_5)_3CCH(CO_2C_2H_5)_2$	—	Na	Ether	851
n-$C_8H_{17}CH(C_6H_5)(CH_2)_3Cl$	n-$C_8H_{17}CH(C_6H_5)(CH_2)_3CH(CO_2C_2H_5)_2$	42	$NaOC_2H_5$	Ethanol	805
Diphenyl-o-tolylmethyl bromide	Diethyl (diphenyl-o-tolylmethyl)malonate	69	$Mg(OC_2H_5)_2$	Ethanol	829
Diphenyl-p-tolylmethyl bromide	Diethyl (diphenyl-p-tolylmethyl)malonate	77	$Mg(OC_2H_5)_2$	Ethanol	829
Diphenyl-o-methoxyphenyl-methyl bromide	Diethyl (diphenyl-o-methoxyphenylmethyl)-malonate	82	$Mg(OC_2H_5)_2$	Ethanol	829
Diphenyl-p-methoxy-phenylmethyl bromide	Diethyl (diphenyl-p-methoxyphenylmethyl)malonate	—	$Mg(OC_2H_5)_2$	Ethanol	829
[structure: phenanthrene/steroid-type ring system with CH_3, $CO_2C_2H_5$, CH_2Br substituents and CH_3O group]	[structure: phenanthrene/steroid-type ring system with CH_3, $CO_2C_2H_5$, $CH_2CH(CO_2C_2H_5)_2$ substituents and CH_3O group]	—	—	—	852

n-$C_{22}H_{45}I$	n-$C_{22}H_{45}CH(CO_2C_2H_5)_2$	92	$NaOC_2H_5$	Ethanol	802, 134, 684
n-$C_8H_{17}CH{=}CH(CH_2)_{12}Br$	n-$C_8H_{17}CH{=}CH(CH_2)_{12}CH(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Ethanol	853
n-$C_6H_{13}CH(C_6H_5)(CH_2)_6Cl$	n-$C_6H_{13}CH(C_6H_5)(CH_2)_6CH(CO_2C_2H_5)_2$	57	$NaOC_2H_5$	Ethanol	805
n-$C_6H_{17}CH(C_6H_5)(CH_2)_7Br$	n-$C_6H_{17}CH(C_6H_5)(CH_2)_7CH(CO_2C_2H_5)_2$	73	$NaOC_2H_5$	Ethanol	805
i-$C_3H_7(CH_2)_{20}I$	i-$C_3H_7(CH_2)_{20}CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	854
n-$C_{10}H_{21}CH(C_{10}H_{21}{-}n)(CH_2)_2I$	n-$C_{10}H_{21}CH(C_{10}H_{21}{-}n)(CH_2)_2CH(CO_2C_2H_5)_2$	16	$NaOC_2H_5$	Ethanol	70
n-$C_7H_{15}CH(CH_3)CH_2CH{=}$ $C(CH_3)(CH_2)_6CH(CH_3)I$	n-$C_7H_{15}CH(CH_3)CH_2CH{=}C(CH_3)(CH_2)_8$-$CH(CH_3)CH(CO_2C_2H_5)_2$	13	$NaOC_2H_5$	Ethanol	855
n-$C_9H_{19}CH{=}C(CH_3)(CH_2)_6$-$CH(CH_3)I$	n-$C_9H_{19}CH{=}C(CH_3)(CH_2)_9CH(CH_3)CH$-$(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	856
Diphenyl-α-naphthylmethyl bromide	Diethyl (diphenyl-α-naphthylmethyl)-malonate	38	$Mg(OC_2H_5)_2$	Ethanol	829
n-$C_9H_{19}CH(CH_3)(CH_2)_2$-$CH(CH_3)(CH_2)_{10}Br$	n-$C_9H_{19}CH(CH_3)(CH_2)_2CH(CH_3)(CH_2)_{10}$-$CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	317
n-$C_3H_7CH{=}C(CH_3)(CH_2)_4$-$CH{=}C(CH_3)(CH_2)_3I$	n-$C_3H_7CH{=}C(CH_3)(CH_2)_4CH{=}C(CH_3)(CH_2)_9$-$CH(CH_3)CH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	856
C_{25}					
Diphenyl-4-biphenylylmethyl bromide	Diethyl (diphenyl-4-biphenylylmethyl)malonate	89	$Mg(OC_2H_5)_2$	Ethanol	829
3β-Cholestanyl p-toluenesulfonato	Diethyl 3α-cholestanylmalonate	—	Na	Toluene	10
3β-Cholesteryl p-toluenesulfonato	Diethyl 3-cholesterylmalonate and diethyl 3,5-cyclo-6-cholestanylmalonate	—	Na	Xylene	21, 22
3β-Cholesteryl p-toluenesulfonato	Diethyl 3α- and 3β-cholesterylmalonate††	—	Na	Toluene	10

Note: References 577–1080 are on pp. 322–331.

†† The ratio of the β-isomer to the α-isomer was about 9 to 1.

TABLE II

ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

X	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
Cl	None	$(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2$	<60	$NaOC_2H_5$	Ethanol	857
	$CHCl_3$	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	231
	$CHBr_3$	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	231
	CH_3I	$(C_2H_5O_2C)_2CHCH(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	231
	4-Imidazoylmethyl chloride hydrochloride	Diethyl [4-(or 5-)-imidazoylmethyl]-chloromalonate	60	$NaOC_2H_5$	Ethanol	209
	$C_6H_5CH_2Cl$	$C_6H_5CH_2CCl(CO_2C_2H_5)_2$	56	$NaOC_2H_5$	Ethanol	208
	o-Xylylene dibromide	$o\text{-}C_6H_4[CH_2CCl(CO_2C_2H_5)_2]_2$	—	$NaOC_2H_5$	Ethanol-other	228
	m-Xylylene dibromide	$m\text{-}C_6H_4[CH_2CCl(CO_2C_2H_5)_2]_2$	100	$NaOC_2H_5$	Ethanol-other	229
	p-Xylylene dibromide	$p\text{-}C_6H_4[CH_2CCl(CO_2C_2H_5)_2]_2$	—	$NaOC_2H_5$	Ethanol-other	229
	p-Carbethoxybenzyl bromide	Diethyl (p-carbethoxybenzyl)-chloromalonate	Fair	—	—	230
NO_2	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(NO_2)(CO_2C_2H_5)_2$	34	KOC_2H_5	Ethanol	183
	$CH_3CH{=}CHCH_2Cl$	$CH_3CH{=}CHCH_2C(NO_2)(CO_2C_2H_5)_2$	25	KOC_2H_5	Ethanol	183
NH_2	CH_3Br	$CH_3C(NH_2)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	858
	CH_3I	$CH_3C(NH_2)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	858
	$(CH_3)_2SO_4$	$CH_3C(NH_2)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	858
	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(NH_2)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	859
	$Br(CH_2)_3Br$	$\begin{array}{c} CH_2\!-\!CHCO_2H \\ \mid \quad\quad \\ CH_2 \quad\quad \\ \diagdown N \diagup \\ \mid \\ H \end{array}$	25	$NaOC_2H_5$	Ethanol	434
	$i\text{-}C_4H_9I$	$i\text{-}C_4H_9C(NH_2)(CO_2C_2H_5)_2$	55	Na	$i\text{-}C_4H_9OCH_3$	859

	Alkyl halide	Product	Yield %	Base	Solvent	Reference
HCONH	$C_6H_5CH_2Br$	$C_6H_5CH_2C(NH_2)(CO_2C_2H_5)_2$	60	Na	Ether	859
	$i\text{-}C_3H_7Br$	$i\text{-}C_3H_7C(NHCHO)(CO_2C_2H_5)_2$	50	NaH	$(CH_3)_2NCHO$	246
	$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	69	NaH	Toluene	860
	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	—	—	—	861
	$Cl(CH_2)_3Br$	$Cl(CH_2)_3C(NHCHO)(CO_2C_2H_5)_2$	—	—	—	436
	$cis\text{-}ClCH{=}CHCH_2Cl$	$cis\text{-}ClCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	84	NaH	Toluene	860
	$trans\text{-}ClCH{=}CHCH_2Cl$	$trans\text{-}ClCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	86	NaH	Toluene	860
	$CH_2{=}CClCH_2Cl$	$CH_2{=}CClCH_2C(NHCHO)(CO_2C_2H_5)_2$	83	NaH	Toluene	246
	$CH_2{=}CBrCH_2Br$	$CH_2{=}CBrCH_2C(NHCHO)(CO_2C_2H_5)_2$	—	—	—	862
	$CH_2{=}CBrCH_2Br$	$CH_2{=}CBrCH_2C(NHCHO)(CO_2C_2H_5)_2$	81	NaH	Toluene	246
	$BrCH{=}CHCH_2Br$	$BrCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	—	—	—	862
	$BrCH{=}CHCH_2Br$	$BrCH{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	73	NaH	$(CH_3)_2NCHO$	860
	$Cl_2C{=}CHCH_2Br$	$Cl_2C{=}CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	83	NaH	$(CH_3)_2NCHO$	860
	$HC{\equiv}CCH_2Br$	$HC{\equiv}CCH_2C(NHCHO)(CO_2C_2H_5)_2$	82	NaH	C_6H_6	246
	$BrCH_2CH{-}CH_2$ (epoxide, O)	$BrCH_2CHCH_2C(NHCHO)(CO_2C_2H_5)_2$ ($O{-}CO$)	—	—	—	436
	$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(NHCHO)(CO_2CH_3)_2$*	37	$NaOCH_3$	CH_3OH	863
	$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(NHCHO)(CO_2C_2H_5)_2$	62	$NaOC_2H_5$	Ethanol	863
	$CH_2{=}CH(CH_2)_2Br$	$CH_2{=}CH(CH_2)_2C(NHCHO)(CO_2C_2H_5)_2$	56	$NaOC_2H_5$	Ethanol	864, 437
	$BrCH_2CO_2CH_3$	$CH_3O_2CCH_2C(NHCHO)(CO_2CH_3)_2$*	47	$NaOCH_3$	CH_3OH	863
	cyclopropyl $CHCH_2Br$	cyclopropyl $CHCH_2C(NHCHO)(CO_2C_2H_5)_2$	53	$NaOC_2H_5$	Ethanol	864
	3-Bromomethylthiophene	Diethyl (3-thenyl)formamidomalonate	80	NaH	C_6H_6	246
	3-Bromomethylthiophene	Diethyl (3-thenyl)formamidomalonate	80	NaH	Toluene	246
	3-Bromomethylthiophene	Diethyl (3-thenyl)formamidomalonate	93	NaH	$(CH_3)_2NCHO$	246
	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(NHCHO)(CO_2CH_3)_2$*	75	$NaOCH_3$	CH_3OH	863
	$p\text{-}CH_3OC_6H_4CH_2Cl$	$p\text{-}CH_3OC_6H_4CH_2C(NHCHO)(CO_2CH_3)_2$*	73	$NaOCH_3$	CH_3OH	863

Note: References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

TABLE II—Continued

ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

X	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
HCONH (cont.)	3-Nitro-4-methoxybenzyl chloride	Diethyl (3-nitro-4-methoxybenzyl)-formamidomalonate	80	NaH	Toluene	246
	2,4-Dimethylbenzyl chloride	Diethyl (2,4-dimethylbenzyl)-formamidomalonate	89	NaH	Toluene	246
	$BrCH=CHCH_2C(NHCHO)$ $(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2C(NHCHO)CH_2$- $CH=CHC(NHCHO)(CO_2C_2H_5)_2$	—	—	—	862
	$(C_6H_5)_2CHBr$	$(C_6H_5)_2CHC(NHCHO)(CO_2C_2H_5)_2$	43	Na	Xylene	865
	1-Chloromethyl-naphthalene	Diethyl (1-naphthylmethyl)-formamidomalonate	96	NaH	Toluene	246
CH₃CONH						
C_1–C_2						
	CH_3I	$CH_3C(NHCOCH_3)(CO_2C_2H_5)_2$	88	$NaOC_2H_5$	Ethanol	232
	$(CH_3)_2SO_4$	$CH_3C(NHCOCH_3)(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	232
	C_2H_5Br	$C_2H_5C(NHCOCH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	232
C_3						
	$n\text{-}C_3H_7Br$	$n\text{-}C_3H_7C(NHCOCH_3)(CO_2C_2H_5)_2$	71	$NaOC_2H_5$	Ethanol	235, 232
	$CH_3S(CH_2)_2Cl$	$CH_3S(CH_2)_2C(NHCOCH_3)(CO_2C_2H_5)_2$	>56	$NaOC_2H_5$	Ethanol	866
	$CH_3S(CH_2)_2Cl$	$CH_3S(CH_2)_2C(NHCOCH_3)(CO_2C_2H_5)_2$	>60	$NaOC_2H_5\text{-}t$	$t\text{-}C_4H_9OH$	866
	$i\text{-}C_3H_7Br$	$i\text{-}C_3H_7C(NHCOCH_3)(CO_2C_2H_5)_2$	37	$NaOC_2H_5$	Ethanol	234
	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	232, 867
	CH_3COCH_2Br	$CH_3COCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	66	$NaOC_2H_5$	C_6H_6	49
	$ClCH=CHCH_2Cl$	$ClCH=CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	60	—	—	449

C₄

n-C₄H₉Br·NaI	n-C₄H₉C(NHCOCH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	442, 232, 235
n-C₄H₉I	n-C₄H₉C(NHCOCH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	232
i-C₄H₉Br	i-C₄H₉C(NHCOCH₃)(CO₂C₂H₅)₂	46	NaOC₂H₅	Ethanol	235, 232
(CH₃)₂N(CH₂)₂Cl	(CH₃)₂N(CH₂)₂C(NHCOCH₃)(CO₂C₂H₅)₂	88	NaOC₂H₅	Toluene	868
CH₃CH=CHCH₂Cl	CH₃CH=CHCH₂C(NHCOCH₃)(CO₂C₂H₅)₂	80	NaOC₂H₅	Ethanol	442
CH₂=C(CH₃)CH₂Cl	CH₂=C(CH₃)CH₂C(NHCOCH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	232
Cl(CH₂)₃CN	NC(CH₂)₃C(NHCOCH₃)(CO₂C₂H₅)₂	22	NaOC₂H₅	Ethanol	447
4-Chloromethylthiazole hydrochloride	Diethyl acetamido-(4-thiazolylmethyl)malonate	53	NaOC₂H₅	Ethanol	450, 446
2-Chloromethylthiazole	2-Amino-3-(2-thiazolyl)propionic acid	29	NaOC₂H₅	Ethanol	446

C₅

n-C₅H₁₁Br	n-C₅H₁₁C(NHCOCH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	232
2-Chloromethylfuran	Diethyl acetamido(furfuryl)malonate	60-70	NaOC₂H₅	Ethanol	452
2-Chloromethylthiophene	Diethyl acetamido-(2-thenyl)malonate	88	NaOC₂H₅	Ethanol	869
2-Chloromethylthiophene	Diethyl acetamido-(2-thenyl)malonate	71	NaH	Toluene	860
2-Bromomethylthiophene	Diethyl acetamido-(2-thenyl)malonate	67	NaOC₂H₅	Ethanol	870
3-Bromomethylthiophene	Diethyl acetamido-(3-thenyl)malonate	85	NaH	Toluene	246
5-Bromo-2-bromomethyl-thiophene	Diethyl acetamido-(5-bromo-2-thenyl)-malonato	60	NaOC₂H₅	Ethanol	870
2-Bromo-3-bromomethyl-thiophene	Diethyl acetamido-(2-bromo-3-thenyl)-malonate	90	NaOC₂H₅	Ethanol	870
5-Chloromethyl-1-methylimidazole hydrochloride	Ethyl α-acetamido-α-carbethoxy-β-(1-methyl-5-imidazolyl)propionate	68	NaOC₂H₅	Ethanol	443

C₆

n-C₆H₁₃I	n-C₆H₁₃C(NHCOCH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	232

Note: References 577-1080 are on pp. 322-331.

TABLE II—Continued

ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

X	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
CH₃CONH (Cont.)	C_7					
	$n\text{-}C_7H_{15}Br$	$n\text{-}C_7H_{15}C(NHCOCH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	232
	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	235
	$o\text{-}FC_6H_4CH_2Cl$	$o\text{-}FC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	89	$NaOC_2H_5$	Ethanol	411
	$m\text{-}FC_6H_4CH_2Cl$	$m\text{-}FC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	08	$NaOC_2H_5$	Ethanol	411
	$p\text{-}FC_6H_4CH_2Cl$	$p\text{-}FC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	76	$NaOC_2H_5$	Ethanol	411
	$o\text{-}ClC_6H_4CH_2Cl$	$o\text{-}ClC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	81	$NaOC_2H_5$	Ethanol	418
	$p\text{-}ClC_6H_4CH_2Cl$	$p\text{-}ClC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	81	$NaOC_2H_5$	Ethanol	418
	2,4-Dichlorobenzyl chloride	$2,4\text{-}Cl_2C_6H_3CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	451
	3,4-Dichlorobenzyl chloride	$3,4\text{-}Cl_2C_6H_3CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	89	$NaOC_2H_5$	Ethanol	418
	$p\text{-}O_2NC_6H_4CH_2Cl$	$p\text{-}O_2NC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	88	$NaOC_2H_5$	Ethanol	448
	$p\text{-}O_2NC_6H_4CH_2Br$	$p\text{-}O_2NC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	100	$NaOC_2H_5$	Ethanol	454
	2-Hydroxy-5-nitrobenzyl chloride	Diethyl acetamido-(2-hydroxy-5-nitrobenzyl)malonate	20	$NaOC_2H_5$	Ethanol	418
	$p\text{-}H_2NC_6H_4CH_2Cl$	$p\text{-}H_2NC_6H_4CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	97	$NaOC_2H_5$	Ethanol	418
	C_8					
	$n\text{-}C_8H_{17}I$	$n\text{-}C_8H_{17}C(NHCOCH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	232
	$C_6H_5S(CH_2)_2Cl$	$C_6H_5S(CH_2)_2CH(NH_2)CO_2H$	>20	$NaOC_2H_5$	Ethanol	457
	3-Nitro-4-methylbenzyl chloride	2-Amino-3-(3-nitro-4-methylphenyl)-propionic acid	34	$NaOC_2H_5$	Ethanol	451
	2-Fluoro-4-methoxybenzyl chloride	Diethyl acetamido-(2-fluoro-4-methoxybenzyl)malonate	85	$NaOC_2H_5$	Ethanol	415
	$C_6H_5COCH_2Br$	$C_6H_5COCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	71	$NaOC_2H_5$	C_6H_6	49, 450

Alkylating agent	Product		Condensing agent	Solvent	Ref.
o-O₂NC₆H₄COCH₂Br	o-O₂NC₆H₄COCH₂C(NHCOCH₃)(CO₂C₂H₅)₂	41	NaOC₂H₅	Ethanol	456
o-O₂NC₆H₄COCH₂Br	o-O₂NC₆H₄COCH₂C(NHCOCH₃)(CO₂C₂H₅)₂	19	NaOC₂H₅	(C₂H₅O)₂CO	49
5-Chloromethyl-1-isopropylimidazole hydrochloride	2-Amino-3-(1-isopropyl-5-imidazolyl)-propionic acid	44	NaOC₂H₅	Ethanol	443
1-Chloromethyl-benzimidazole hydrochloride	2-Amino-3-(1-benzimidazolyl)propionic acid	—	NaOC₂H₅	Ethanol	455
2-Chloromethyl-benzimidazole hydrochloride	Diethyl acetamido-(2-benzimidazolyl-methyl)malonate	65	NaOC₂H₅	Ethanol	455
C_9					
n-C₉H₁₉Br	n-C₉H₁₉C(NHCOCH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	232
2-Ethoxy-5-nitrobenzyl chloride	Diethyl acetamido-(2-ethoxy-5-nitrobenzyl)malonate	82	NaOC₂H₅	Ethanol	448
2-Bromo-3-bromomethylcoumarone	Diethyl acetamido-(2-bromo-3-coumaronylmethyl)malonate	73	NaOC₂H₅	Ethanol	440
2-Chloromethyl-4-methylbenzimidazole hydrochloride	Ethyl 2-acetamido-3-(4-methyl-2-benzimidazolyl)propionate	40	NaOC₂H₅	Ethanol	455
2-Chloromethyl-5-methyl-benzimidazole hydrochloride	Ethyl 2-acetamido-3-(5-methyl-2-benzimidazolyl)propionate	50	NaOC₂H₅	Ethanol	455
C_{10}					
β-3-Indolylethyl bromide	Diethyl acetamido-[β(3-indolyl)-ethyl]malonate	58	NaOC₂H₅	Ethanol	441
5-Chloromethyl-1-cyclohexylimidazole hydrochloride	2-Amino-3-(1-cyclohexyl-5-imidazolyl)-propionic acid	49	NaOC₂H₅	Ethanol	443

Note: References 577–1080 are on pp. 322–331.

TABLE II—Continued

ALKYLATION OF CHLORO-, NITRO-, AMINO- AND ACYLAMINO-MALONIC ESTERS, $XCH(CO_2R)_2$

(The diethyl ester was used unless otherwise specified.)

X	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
CH_3CONH (Cont.)	5-Chloromethyl-1-phenylimidazole hydrochloride	2-Amino-3-(1-phenyl-5-imidazolyl)-propionic acid	49	$NaOC_2H_5$	Ethanol	443
	2-Chloromethyl-5,6-dimethylbenzimidazole hydrochloride	Ethyl 2-acetamido-3-(5,6-dimethyl-2-benzimidazolyl)propionate	ca. 40	$NaOC_2H_5$	Ethanol	455
C_{11}						
	$C_6H_5CH(CO_2C_2H_5)CH_2Br$	$C_6H_5CH(CO_2C_2H_5)CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	—	—	—	439
	1-Chloromethylnaphthalene	Diethyl acetamido-(1-naphthylmethyl)malonate	92	$NaOC_2H_5$	Ethanol	440
	5-Chloromethyl-1-benzylimidazole hydrochloride	2-Amino-3-(1-benzyl-5-imidazolyl)propionic acid	45	$NaOC_2H_5$	Ethanol	443
C_{13}–C_{14}						
	4-(4-Nitrophenyl-sulfonyl)benzyl bromide	Diethyl acetamido-[4-(4-nitrophenylsulfonyl)benzyl]malonato	74	$NaOC_2H_5$	Ethanol-dioxane	454
	3,5-Diiodo-4-(4-methoxyphenyl-sulfonyl)benzyl chloride	Diethyl acetamido-[3,5-diiodo-4-(4-methoxyphenylsulfonyl)benzyl]-malonato	84	$NaOC_2H_5$	Ethanol-dioxane	438

			Yield %			References
C_6H_5CONH	$C_3–C_8$					
	$i\text{-}C_3H_7I$	$C_6H_5CONHC(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	66	$NaOC_2H_5$	Ethanol	233
	$i\text{-}C_4H_9I$	$C_6H_5CONHC(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	74	$NaOC_2H_5$	Ethanol	233
	$ClCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(NHCOC_6H_5)(CO_2C_2H_5)_2$	88	$NaOC_2H_5$	Ethanol	233
	$Br(CH_2)_2CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_2C(NHCOC_6H_5)(CO_2C_2H_5)_2$	90	$NaOC_2H_5$	Ethanol	459
	2-Chloromethylpyridine	2-Amino-3-(2-pyridyl)propionic acid	17	$NaOC_2H_5$	Ethanol	458
	$C_6H_5CH_2Cl$	$C_6H_5CONHC(CH_2C_6H_5)(CO_2C_2H_5)_2$	95	$NaOC_2H_5$	Ethanol	233
	$p\text{-}HOC_6H_4(CH_2)_2Br$	$p\text{-}HOC_6H_4(CH_2)_2CH(NH_2)CO_2H$	7	$NaOC_2H_5$	Ethanol	453
Phthal-imido	$C_2–C_3$					
($=C_8H_4O_2N$)	CH_3OCH_2Cl	$CH_3OCH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$	73	Na	C_6H_6	871
	$ClCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$	95–99	$NaOC_2H_5$	$ClCH_2CO_2C_2H_5$	467
	$ClCH_2SCH_2Cl$	$(C_2H_5O_2C)_2C(C_8H_4O_2N)CH_2S\text{-}CH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$	81	Na	Xylene	460
	$C_4–C_{11}$					
	$CH_3S(CH_2)_2Cl$	$CH_3S(CH_2)_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$	76–80	$NaOC_2H_5$	None	466, 465
	$CH_2{=}CHCH_2I$	$CH_2{=}CHCH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$	90	$NaOC_2H_5$	None	462, 435
	$Br(CH_2)_3Br$	$(C_2H_5O_2C)_2C(C_8H_4O_2N)(CH_2)_3C(C_8H_4O_2N)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	None	462, 236, 463
	$C_2H_5S(CH_2)_2Cl$	$C_2H_5S(CH_2)_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$	68	Na	None	461
	$Cl(CH_2)_3CN$	$NC(CH_2)_3C(C_8H_4O_2N)(CO_2C_2H_5)_2$	75–80	$NaOC_2H_5$	None	462
	2-Chloromethylthiophene	Diethyl phthalimido(2-thenyl)malonate	93	Na	Toluene	869
	2-Chloromethylpyridine	Diethyl phthalimido-(2-pyridylmethyl)-malonate	10	Na	Xylene	468
	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_8H_4O_2N)(CO_2C_2H_5)_2$	75–80	$NaOC_2H_5$	None	462
	γ-Bromopropylphthalimide	Diethyl (γ-phthalimidopropyl)-phthalimidomalonate	75	Na	None	236, 462

Note: References 577–1080 are on pp. 322–331.

TABLE III

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_1 CH₃	**C_1**					
	CH₃I	(CH₃)₂C(CO₂C₂H₅)₂	55	KOH	None	82
	CH₃I	(CH₃)₂C(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	571
	CH₂I₂	CH₂[C(CH₃)(CO₂C₂H₅)₂]₂	—	NaOC₂H₅	Ethanol	872
	CHCl₃	Cl₂CHC(CH₃)(CO₂C₂H₅)₂, and (C₂H₅O₂C)₂C(CH₃)CHClCC(CH₃)(CO₂C₂H₅)₂	—	Na	Ether	231
	CHCl₃	Cl₂CHCH(CH₃)(CO₂C₂H₅)₂, and (C₂H₅O₂C)₂C(CH₃)CHClCC(CH₃)(CO₂C₂H₅)₂	—	K	Ether	231
	CHBr₃	Br₂CHC(CH₃)(CO₂C₂H₅)₂, and (C₂H₅O₂C)₂C(CH₃)CHBrC(CH₃)(CO₂C₂H₅)₂	—	Na	Ether	231
	CHI₃	I₂CHC(CH₃)(CO₂C₂H₅)₂, and (C₂H₅O₂C)₂C(CH₃)CHIC(CH₃)(CO₂C₂H₅)₂	—	Na	Ether	231
	C_2					
	C₂H₅I	C₂H₅C(CH₃)(CO₂C₂H₅)₂	51	NaOC₂H₅	Ethanol	577
	CH₃SCH₂Cl	CH₃SCH₂C(CH₃)(CO₂C₂H₅)₂	70	Na	Ether	205
	CH₂ClCH₂Br	Cl(CH₂)₂C(CH₃)(CO₂C₂H₅)₂	15	Na	Toluene	873
	CH₂BrCH₂Br	{ Br(CH₂)₂C(CH₃)(CO₂C₂H₅)₂, CH₂C(CH₃)(CO₂C₂H₅)₂ }	70	NaOC₂H₅	Ethanol	874, 172; 626
	CH₂BrCH₂Br	Br(CH₂)₂C(CH₃)(CO₂C₂H₅)₂	32	Na	C₆H₆	875
	C_3					
	n-C₃H₇I	n-C₃H₇C(CH₃)(CO₂C₂H₅)₂	87	NaOC₂H₅	Ethanol	582, 488
	Not stated	n-C₃H₇C(CH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	571
	C₂H₅SCH₂Cl	C₂H₅SCH₂C(CH₃)(CO₂C₂H₅)₂	64	Na	Ether	205

					References
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
Not stated	$i\text{-}C_3H_7C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	571
$Br(CH_2)_3Br$	$Br(CH_2)_3C(CH_3)(CO_2C_2H_5)_2$	45	Na	—	629, 172
$(CH_3)_2CClNO_2$	$(CH_3)_2C(NO_2)C(CH_3)(CO_2C_2H_5)_2$	87–89	—	Ether	556
$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(CH_3)(CO_2C_2H_5)_2$	—	Na	Ether	876, 571
$ClCH_2CO_2C_2H_5$	Diethyl α-carbethoxy-α-methylsuccinate	—	Na	C_6H_6	653, 101
$ClCH_2CO_2C_2H_5$	Diethyl α-carbethoxy-α-methylsuccinate				653
C_4					
Not stated	$n\text{-}C_4H_9C(CH_3)(CO_2C_2H_5)_2$	—	Na	—	571
$C_2H_5SCH(CH_3)Cl$	$C_2H_5SCH(CH_3)C(CH_3)(CO_2C_2H_5)_2$*	43	Na	Ether	205
$CH_3CCl{=}CHCH_2Cl$	$CH_3CCl{=}CHCH_2C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	533
C_5					
$n\text{-}C_5H_{11}Br$	$n\text{-}C_5H_{11}C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	551
$n\text{-}C_3H_7CH(CH_3)Br$	$n\text{-}C_3H_7CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	551
$i\text{-}C_5H_{11}Br$	$i\text{-}C_5H_{11}C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	551
$n\text{-}C_4H_9SCH_2Cl$	$n\text{-}C_4H_9SCH_2C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$CH_3CHBrCO_2C_2H_5$	Diethyl α,α'-dimethyl-α-carbethoxysuccinate	—	Na	None	877
$CH_3CHBrCO_2C_2H_5$	Diethyl α,α'-dimethyl-α-carbethoxysuccinate	37	$NaOC_2H_5$	Ethanol	223, 702
$ClCH(CO_2C_2H_5)_2$	$(CH_3O_2C)_2CHCH(CO_2C_2H_5)_2$* and $(CH_3O_2C)_2C{=}C(CO_2C_2H_5)_2$*	—	$NaOCH_3$	CH_3OH	752
Cyclobutylmethyl tosylate	Diethyl (cyclobutylmethyl)-methylmalonate	18	$NaOC_2H_5$	Ethanol	334
α-Chloromethylthiophene	Diethyl (α-thenyl)methylmalonate	Good	—	—	878
C_6					
$n\text{-}C_6H_{13}Br$	$n\text{-}C_6H_{13}C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	551
$i\text{-}C_6H_{13}I$	$i\text{-}C_6H_{13}C(CH_3)(CO_2C_2H_5)_2$	83	Na	C_6H_6	247
$n\text{-}C_4H_9CH(CH_3)Br$	$n\text{-}C_4H_9CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	551
$n\text{-}C_4H_9S(CH_2)_2Cl$	$n\text{-}C_4H_9S(CH_2)_2C(CH_3)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	553
$C_2H_5CHBrCO_2C_2H_5$	Diethyl α-methyl-α'-ethyl-α-carbethoxysuccinate	20	$NaOC_2H_5$	Ethanol	223, 162
$(CH_3)_2CBrCO_2C_2H_5$	Diethyl α,α,α'-trimethyl-α'-carbethoxysuccinate	57	Na	None	872, 162, 223

Note: References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
CH₃ (cont.)	2'-Cyclohexenyl bromide	Diethyl (2-cyclohexenyl)methylmalonate	73	NaOC₂H₅	Ethanol	319
	1,2-Dibromocyclohexane	Diethyl (2-cyclohexenyl)methylmalonate	>90	NaOC₂H₅	Ethanol	310, 150
	C₇					
	i-C₃H₇CHBrCO₂C₂H₅	Diethyl α-isopropyl-α'-methyl-α'-carbethoxysuccinate	8	NaOC₂H₅	Ethanol	223
	ClCH(CO₂C₂H₅)₂	(C₂H₅O₂C)₂CHCH(CH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	752
	BrCH(CO₂C₂H₅)₂	[(C₂H₅O₂C)₂CHCH(CH₃)]C=C(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	752
	β-(2-Cyclopentenyl)ethyl bromide	Diethyl methyl-[β-(2-cyclopentenyl)-ethyl]malonate	56	NaOC₂H₅	Ethanol	334
	β-(2-Cyclopentenyl)ethyl tosylate	Diethyl methyl-[β-(2-cyclopentenyl)-ethyl]malonate	56	NaOC₂H₅	Ethanol	334
	Cyclohexylmethyl iodide	Diethyl methyl(cyclohexylmethyl)-malonate	—	NaOC₂H₅	Ethanol	334
	Cyclohexylmethyl iodide	Diethyl methyl(cyclohexylmethyl)malonate	65	NaOC₄H₉-n	n-C₄H₉OH	334
	C₆H₅CH₂Cl	C₆H₅CH₂C(CH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	615
	C₈					
	n-C₈H₁₇I	n-C₈H₁₇C(CH₃)(CO₂C₂H₅)₂	63	NaOC₂H₅	Ethanol	870
	n-C₄H₉CH(C₂H₅)CH₂Br	n-C₄H₉CH(C₂H₅)CH₂C(CH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	551
	(CH₃)₂CBr(CH₂)₂CO₂C₂H₅	C₂H₅O₂C(CH₂)₂C(CH₃)₂C(CH₃)(CO₂C₂H₅)₂	0	NaOC₂H₅	Ethanol	880
	ClCH₂CCl(CO₂C₂H₅)₂	(C₂H₅O₂C)₂C(CH₃)C(CH₃)(CO₂C₂H₅)₂	5	NaOC₂H₅	Ethanol	578
	α-Chloroethylcyclohexyl sulfide	Diethyl [α-(cyclohexylthio)-ethyl]methylmalonate	70–90	NaOC₂H₅	Toluene	126
	β-(1-Cyclohexenyl)ethyl bromide	Diethyl methyl-[β-(1-cyclohexenyl)-ethyl]malonate	53	K	C₆H₆	426
	C₆H₅(CH₂)₂Br	C₆H₅(CH₂)₂C(CH₃)(CO₂C₂H₅)₂	60	K	Xylene	881
	C₆H₅O(CH₂)₂Br	C₆H₅O(CH₂)₂C(CH₃)(CO₂C₂H₅)₂	65	Na	Toluene	873, 758

C₉

Halide	Product	Yield %	Condensing agent	Solvent	Reference
n-C₉H₁₉I	n-C₉H₁₉C(CH₃)(CO₂C₂H₅)₂	94	—	—	882
Br(CH₂)₃CH(C₂H₅)CO₂C₂H₅	C₂H₅O₂CCH(C₂H₅)(CH₂)₃C(CH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	814
C₆H₅O(CH₂)₃Cl	C₆H₅O(CH₂)₃C(CH₃)(CO₂C₂H₅)₂	—	NaOCH₃	CH₃OH	581
o-CH₃C₆H₄(CH₂)₂Br	o-CH₃C₆H₄(CH₂)₂C(CH₃)(CO₂C₂H₅)₂	50	Na	C₆H₆	883
p-CH₃C₆H₄(CH₂)₂Br	p-CH₃C₆H₄(CH₂)₂C(CH₃)(CO₂C₂H₅)₂	87	Na	C₆H₆	416
p-CH₃C₆H₄(CH₂)₂Br	p-CH₃C₆H₄(CH₂)₂C(CH₃)(CO₂C₂H₅)₂	35	NaOC₂H₅	Ethanol	423

C₁₀

Halide	Product	Yield %	Condensing agent	Solvent	Reference
Geranyl chloride	Diethyl methyl(geranyl)malonate	50	NaOC₂H₅	Ethanol	31
C₆H₅CH₂SCH₂CH(CH₃)Br	C₆H₅CH₂SCH₂CH(CH₃)C(CH₃)(CO₂C₂H₅)₂	50	NaOC₂H₅	Ethanol	794
β-(2,3-Dimethylphenyl)ethyl bromide	Diethyl methyl-[β-(2,3-dimethylphenyl)-ethyl]malonate	50	Na	C₆H₆	417
β-(2,4-Dimethylphenyl)ethyl bromide	Diethyl methyl-[β-(2,4-dimethylphenyl)-ethyl]malonate	56	Na	C₆H₆	417
p-C₂H₅C₆H₄COCH₂Cl	p-C₂H₅C₆H₄COCH₂C(CH₃)(CO₂C₂H₅)₂	12	Na	Ether	420
C₆H₅CHBrCO₂C₂H₅	C₆H₅CH(CO₂C₂H₅)C(CH₃)(CO₂C₂H₅)₂	45	Na	None	583
m-Carbethoxybenzyl chloride	Diethyl methyl-(m-carbethoxybenzyl)-malonate	—	—	—	230
β-Bromoethylphthalimide	Diethyl methyl-(β-phthalimidoethyl)-malonate	40–46	Na	C₆H₆	884

C₁₁

Halide	Product	Yield %	Condensing agent	Solvent	Reference
Chloromethyltetralin†	Diethyl methyl(tetrahydronaphthyl-methyl)malonate	51	Na	C₆H₆	410
α-Chloromethylnaphthalene	Diethyl methyl-(α-naphthylmethyl)-malonate	71	NaOC₂H₅	Ethanol	885, 886
β-Chloromethylnaphthalene	Diethyl methyl-(β-naphthylmethyl)-malonate	—	—	—	886

C₁₂–C₂₄

Halide	Product	Yield %	Condensing agent	Solvent	Reference
n-C₁₂H₂₅X‡	n-C₁₂H₂₅C(CH₃)(CO₂C₂H₅)₂	—	—	—	887
n-C₁₃H₂₇X‡	n-C₁₃H₂₇C(CH₃)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	888
n-C₁₄H₂₉X‡	n-C₁₄H₂₉C(CH₃)(CO₂C₂H₅)₂	—	—	—	887

Note: References 577–1080 are on pp. 322–331.

† This halide was probably a mixture of isomers.

‡ The halogen was not specified.

Halide	Product	Metal reagent	Conversion (yield)	Solvent	Reference
CH_2BrCH_2Br	$CH_2 \cdot CH_2(C_2H_5)CO_2C_2H_5$ (O——CO)	—	—	—	555
CH_2BrCH_2Br	$Br(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	—	Ethanol	172
$BrCH=CHBr$	$\{BrCH=CHC(C_2H_5)(CO_2C_2H_5)_2$ / $3,6,6$-Tricarbethoxy-3-octene$\}$	Na	25, 31	Ether	54
C_5					
$CH_3O(CH_2)_2Cl$	$CH_3O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$	Na	—	Ether	374
$C_2H_5OCH_2Cl$	$C_2H_5OCH_2C(C_2H_5)(CO_2C_2H_5)_2$	Na	74	Ether	542
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	61	Toluene	205
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_2H_5)(CO_2C_2H_5)_2$	Na	—	Ether	125
CH_3COCH_2Cl	$CH_3COCH_2C(C_2H_5)(CO_2C_2H_5)_2$	Na	—	Ether	891
CH_3COCH_2Cl	$CH_3COCH_2C(C_2H_5)(CO_2C_2H_5)_2$	Na	—	C_6H_6	891
$i\text{-}C_3H_7I$	$i\text{-}C_3H_7 \cdot C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	46 (75)§	Ethanol	145
$CH_2=CHCH_2Cl$	$CH_2=CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	70–80	Ethanol	558
$Cl(CH_2)_3Br$	$Cl(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	—	Ethanol	814
$Cl(CH_2)_3I$	$I(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	46	Ethanol	92
$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	Na	32	C_6H_6	537, 656
$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	—	Ethanol	814
$(CH_3)_2CCNO_2$	$\{(CH_3)_2CNO_2C(C_2H_5)(CO_2C_2H_5)_2$ / $(CH_3)_2CHC(C_2H_5)(CO_2C_2H_5)_2\}$	Na	40 (65)§ / 8 (13)§	Ether	177
$cis\text{-}ClCH=CHCH_2Cl$	$cis\text{-}ClCH=CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	70–80	Ethanol	558
$trans\text{-}ClCH=CHCH_2Cl$	$trans\text{-}ClCH=CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	70–80	Ethanol	558, 621
$CH_2=CClCH_2Cl$	$CH_2=CClC(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	70–80	Ethanol	558
C_4					
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	ca. 80	Ethanol	536
$n\text{-}C_4H_9I$	$n\text{-}C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$	$NaOC_2H_5$	62	Ethanol	390, 892
$(C_4H_9O\text{-}n)_2CO$	$n\text{-}C_4H_9C(C_2H_5)(CO_2C_4H_9\text{-}n)_2$¶	$NaOC_2H_5$	42 (68)§	$(n\text{-}C_4H_9O)_2CO$	890, 330
$CH_3O(CH_2)_3Cl$	$CH_3O(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$*	$NaOCH_3$	—	Methanol	814
$(C_4H_9O\text{-}i)_2CO$	$i\text{-}C_4H_9C(C_2H_5)(CO_2C_4H_9\text{-}i)_2$‖	$NaOC_4H_9\text{-}i$	45 (70)§	$(i\text{-}C_4H_9O)_2CO$	890, 330

Note: References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

‡ The halogen was not specified.

§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

¶ The diisobutyl ester was used in this experiment.

‖ The di-n-butyl ester was used in this experiment.

TABLE III —Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, RCH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_2H_5 (cont.)	$C_2H_5CHClCH(CH_3)Br$	$C_2H_5CHClCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$	ca. 80	$NaOC_2H_5$	Ethanol	630, 118
	$(CH_3)_2CBr$	$(CH_3)_2C(C_2H_5)(CO_2C_2H_5)_2$	+	Na	Toluene	15
	$CH_2=C(CH_2CH_2)Cl$	$C(CH_3)CH_2C(C_2H_5)(CO_2C_2H_5)_2$	70–80	$NaOC_2H_5$	Ethanol	558
	$CH_3—CHCH—CH_2$ O	$CH_3—CHCHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	11
		$O——CO$				
	$n-C_3H_7OCH_2Cl$	$n-C_3H_7OCH_2C(C_2H_5)(CO_2C_2H_5)_2$	50	Na	Ether	542
	$C_2H_5O(CH_2)_3Cl$	$C_2H_5O(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaNH_2$	—	351
	$C_2H_5OCH(CH_3)Cl$	$C_2H_5OCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$	60	$NaNH_2$	C_6H_6,ether	203
	$CH_3—CHO(CH_2)_3Cl$	$CH_3—CHO(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	10–45	$NaOC_2H_5$	Ethanol	511
	$n-C_3H_7SCH_2Cl$	$n-C_3H_7SCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$C_2H_5SCH(CH_3)Cl$	$C_2H_5SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	126
	$C_2H_5SCH(CH_3)Cl$	$C_2H_5SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$	73	Na	Ether	205
	$i-C_3H_7SCH_2Cl$	$i-C_3H_7SCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$CH_2—CHCH_2SCH_2Cl$	$CH_2—CHCH_2SCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125, 893
	$CH_2CCl—CHCH_2Cl$	$CH_3Cl=CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	70–80	$NaOC_2H_5$	Ethanol	558
	$C_2H_5OCHBrCH_2Br$	$CH_2CHOCH_2H_3C(C_2H_5)CO_2C_2H_5$ $O——CO$	60	$NaNH_2$	Ether	277
	$ClCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	Ether	653, 101, 891
	$ClCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	C_6H_6	653, 891
	$BrCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	Ether	891
	$BrCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	C_6H_6	891
C_3	$n-C_3H_7Br$	$n-C_3H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	543, 895
	$i-C_3H_7Br$	$i-C_3H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	75	Na	Toluene	51
	$i-C_3H_7Br$	$i-C_3H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	ca. 80	$NaOC_2H_5$	Ethanol	536
	$i-C_3H_7Br$	$i-C_3H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44, 51, 227

Halide	Ester or Nitrile	Yield %	Base	Solvent	References
(i-C₅H₁₁O)₂CO	i-C₅H₁₁C(C₂H₅)(CO₂C₅H₁₁-i)₂**	60	KOC₅H₁₁-i	(i-C₅H₁₁O)₂CO	890, 330
n-C₄H₉CH(CH₃)Br	n-C₄H₉CH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	617
(+)-n-C₃H₇CH(CH₃)Br	(+)-n-C₃H₇CH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	549
(−)-n-C₃H₇CH(CH₃)Br	(−)-n-C₃H₇CH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	549
(C₂H₅)₂CHBr	(C₂H₅)₂CHC(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	617, 148
(C₂H₅)₂CHOSO₂C₆H₄CH₃-p?	(C₂H₅)₂CHC(C₂H₅)(CO₂C₂H₅)₂	Poor	Na	C₆H₆	238
[(C₂H₅)₂CHO]₂CO	(C₂H₅)₂CHC(C₂H₅)(CO₂C₂H₅)₂	35	KOCH(C₂H₅)₂	[(C₂H₅)₂CHO]₂CO	890, 330
C₂H₅CH(CH₃)CH₂Br	C₂H₅CH(CH₃)CH₂C(C₂H₅)(CO₂C₂H₅)₂	30	NaOC₂H₅	Ethanol	148
C₂H₅C(CH₃)₂Br	C₂H₅C(CH₃)₂C(C₂H₅)(CO₂C₂H₅)₂	5	NaOC₂H₅	Ethanol	15
CH₃CH=CHCH(CH₃)Br	CH₃CH=CHCH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	547
(CH₃)₂C=CHCH₂Br	(CH₃)₂C=CHCH₂C(C₂H₅)(CO₂C₂H₅)₂	62	NaOC₂H₅	Ethanol	557
n-C₄H₉OCH₂Cl	n-C₄H₉OCH₂C(C₂H₅)(CO₂C₂H₅)₂	50	Na	Ether	542
i-C₄H₉OCH₂Cl	i-C₄H₉OCH₂C(C₂H₅)(CO₂C₂H₅)₂	56	Na	Ether	542
n-C₄H₉OCH(CH₃)Cl	n-C₄H₉OCH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	62	NaNH₂	C₆H₅-ether	203
(CH₃)₃COCH₂Cl	(CH₃)₃COCH₂C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
n-C₄H₅SCH₂Cl	n-C₄H₅SCH₂C(C₂H₅)(CO₂C₂H₅)₂	70-75	NaOC₂H₅	Toluene	125
C₂H₅CH(CH₃)SCH₂Cl	C₂H₅CH(CH₃)SCH₂C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125, 893
i-C₄H₅SCH₂Cl	i-C₄H₅SCH₂C(C₂H₅)(CO₂C₂H₅)₂	30	NaOC₂H₅	Toluene	125
C₂H₅SCH₂CH(CH₃)Cl	C₂H₅SCH₂CH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	Na	Toluene	554
CH₃CHBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	162
CH₃CHBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	Na	Ether	223
I(CH₂)₂CO₂C₂H₅	C₂H₅O₂C(CH₂)₂C(C₂H₅)(CO₂C₂H₅)₂	—	Na	C₆H₆	894
I(CH₂)₃CO₂C₂H₅	C₂H₅O₂C(CH₂)₃C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	894
Cyclobutylmethyl tosylate	Diethyl ethyl(cyclobutylmethyl)malonate	65	NaOC₂H₅	Ethanol	334
Cyclopentyl bromide	Diethyl ethyl(cyclopentyl)malonate	—	Na	Toluene	890
Cyclopentyl bromide	Diethyl ethyl(cyclopentyl)malonate	—	NaOC₂H₅	Ethanol	617
Tetrahydrofurfuryl bromide	Diethyl ethyl(tetrahydrofurfuryl)malonate	—	NaOC₂H₅	Ethanol	543
2-Chlorotetrahydropyran	Diethyl ethyl-(2-tetrahydropyranyl)-malonate	—	NaH	Toluene	683
2-Chloromethylthiophene	Diethyl ethyl-(2-thenyl)malonate	—	Na	None	897
2-Methyl-4-chloro-methylthiazole	Diethyl ethyl-(2-methyl-4-thiazolyl-methyl)malonate	59	NaOC₂H₅	Ethanol	548
C₆					
n-C₆H₁₃Br	n-C₆H₁₃CH(C₂H₅)(CO₂C₂H₅)₂	64	NaOC₂H₅	Ethanol	538
n-C₄H₉CH(CH₃)Br	n-C₄H₉CH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	617
n-C₃H₇CH(C₂H₅)X‡	n-C₃H₇CH(C₂H₅)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	547

Note: References 577–1080 are on pp. 322–331.

** The diisoamyl ester was used in this experiment.

‡ The halogen was not specified.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

$R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

R' (Cont.)	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C₃H₇ (Cont.)	n-C₃H₇CH(CH₃)CH₂Br	n-C₃H₇CH(CH₃)CH₂C(C₃H₇)(CO₂C₂H₅)₂	33–43	NaOC₂H₅	Ethanol	148,550
	i-C₄H₉Br	i-C₄H₉C(C₃H₇)(CO₂C₂H₅)₂	34	NaOC₂H₅	Ethanol	718,550
	(C₂H₅)₂CHCH₂Br	(C₂H₅)₂CHCH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	748
	i-C₄H₉CH(CH₃)Br	i-C₄H₉CH(CH₃)C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	550
	(CH₃)₃CCH₂Br	(CH₃)₃CCH₂C(C₃H₇)(CO₂C₂H₅)₂	14	NaOC₂H₅	Ethanol	090
	CH₂=CHCH(CH₃)CH₂X	CH₂=CHCH(CH₃)CH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	547
	CH₂=C(CH₃)CH(CH₃)CH₂Cl	CH₂=C(CH₃)CH(CH₃)CH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	898
	n-C₃H₇OCH₂Cl	n-C₃H₇OCH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	374
	n-C₃H₇OCH(CH₃)Cl	n-C₃H₇OCH(CH₃)C(C₃H₇)(CO₂C₂H₅)₂	70	NaNH₂	C₆H₅ ether	203
	n-C₃H₁₁SCH₂Cl	n-C₃H₁₁SCH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	i-C₃H₁₁SCH₂Cl	i-C₃H₁₁SCH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	n-C₃H₇CH(CH₃)SCH₂Cl	n-C₃H₇CH(CH₃)SCH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	n-C₃H₇S(CH₂)₃Cl	n-C₃H₇S(CH₂)₃C(C₃H₇)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	553
	n-C₃H₇SCH(CH₃)₄-n)Cl	n-C₃H₇SCH(CH₃)C(C₃H₇)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	120,809
	C₃H₅SCH((CH₃)₃-n)C(C₃H₇)Cl	C₃H₅SCH(C₃H₇)C(C₃H₇)(CO₂C₂H₅)₂	30–10	NaOC₂H₅	Toluene	120
	C₃H₅S(CH(C₃H₇)₃-i)Cl	C₃H₅S(CH(C₃H₇)₃)C(C₃H₇)(CO₂C₂H₅)₂	30–10	NaOC₂H₅	Toluene	120,809
	i-C₃H₅SCH(C₃H₇)CH₂Cl	i-C₃H₅SCH(C₃H₇)CH₂C(C₃H₇)(CO₂C₂H₅)₂	30–40	NaOC₂H₅	Toluene	120,809
	C₂H₅O₂CCH(C₂H₅)Cl	C₂H₅O₂CCH(C₂H₅)C(C₃H₇)(CO₂C₂H₅)₂	—	Na	None	102
	C₂H₅CH(CO₂C₂H₅)₂	C₂H₅O₂CCH(C₂H₅)C(C₃H₇)(CO₂C₂H₅)₂	23	NaOC₂H₅	Ethanol	223
	(CH₃)₂CHCO₂C₂H₅	C₂H₅O₂CCC(CH₃)₂C(C₃H₇)(CO₂C₂H₅)₂	—	Na	None	102
	(CH₃)₂CHCO₂C₂H₅	C₂H₅O₂CC(CH₃)₂C(C₃H₇)(CO₂C₂H₅)₂	22	NaOC₂H₅	Ethanol	223
	(C₂H₅)₂NCOCH₂Cl	(C₂H₅)₂NCOCH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	530
	Cyclopentylmethyl tosylate	Diethyl ethyl(cyclopentylmethyl)malonate	60	NaOC₂H₅	Ethanol	334
C₇						
(n-C₃H₇)₂CHCH₂Br	(n-C₃H₇)₂CHCH₂C(C₃H₇)(CO₂C₂H₅)₂		31	NaOC₂H₅	Ethanol	148,550
	C₂H₅CH(CH₃)CH₂CH(CH₃)Br	C₂H₅CH(CH₃)CH₂CH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	017
	i-C₄H₉CHClCH₃Br	i-C₄H₉CH(OH₃)CC₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	550
	i-C₃H₇CH(CH₃)CH₂Br	i-C₃H₇CH(CH₃)CH₂C(C₃H₇)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	550

$i\text{-}\mathrm{C_5H_{11}OCH(CH_3)Cl}$	$i\text{-}\mathrm{C_5H_{11}OCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2}$	71	$\mathrm{NaNH_2}$	$\mathrm{C_6H_6}$-ether	203
$n\text{-}\mathrm{C_6H_{13}SCH_2Cl}$	$n\text{-}\mathrm{C_6H_{13}SCH_2C(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Toluene	125, 893
$n\text{-}\mathrm{C_5H_{11}S(CH_2)_2Cl}$	$n\text{-}\mathrm{C_5H_{11}S(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2}$	70–90	$\mathrm{NaOC_2H_5}$	Toluene	553
$n\text{-}\mathrm{C_5H_{11}SCH(CH_3)Cl}$	$n\text{-}\mathrm{C_5H_{11}SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2}$	70–90	$\mathrm{NaOC_2H_5}$	Toluene	120
$i\text{-}\mathrm{C_5H_{11}SCH(CH_3)Cl}$	$i\text{-}\mathrm{C_5H_{11}SCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2}$	70–90	$\mathrm{NaOC_2H_5}$	Toluene	126
$\mathrm{C_2H_5CH(C_2H_5)CH_2SCH_2Cl}$	$\mathrm{C_2H_5CH(C_2H_5)CH_2SCH_2C(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Toluene	125
$n\text{-}\mathrm{C_3H_7CH(CH_3)S(CH_2)_2Cl}$	$n\text{-}\mathrm{C_3H_7CH(CH_3)S(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2}$	70–90	$\mathrm{NaOC_2H_5}$	Toluene	553
$n\text{-}\mathrm{C_4H_9SCH_2CH(CH_3)Cl}$	$n\text{-}\mathrm{C_4H_9SCH_2CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2}$	70–75	$\mathrm{NaOC_2H_5}$	Toluene	554
$n\text{-}\mathrm{C_4H_9SCH(C_2H_5)Cl}$	$n\text{-}\mathrm{C_4H_9SCH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2}$	30–40	$\mathrm{NaOC_2H_5}$	Toluene	126
$i\text{-}\mathrm{C_5H_{11}CHBrCO_2C_2H_5}$	$\mathrm{C_2H_5O_2CCH(C_2H_5\text{-}}i\mathrm{)C(C_2H_5)(CO_2C_2H_5)_2}$	Poor	$\mathrm{NaOC_2H_5}$	Ethanol	223
$\mathrm{C_2H_5O_2C(CH_2)_4I}$	$\mathrm{C_2H_5O_2C(CH_2)_4C(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Ethanol	777
$\mathrm{CHCl(CO_2C_2H_5)_2}$	$\mathrm{(C_2H_5O_2C)_2CHC(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Ethanol	260
β-Cyclopentylethyl bromide	Diethyl ethyl-(β-cyclopentylethyl)malonate	50–60	$\mathrm{NaOC_2H_5}$	Ethanol	725
β-(2-Cyclopentenyl)ethyl bromide	Diethyl ethyl-[β-(2-cyclopentenyl)ethyl]-malonate	46	$\mathrm{NaOC_2H_5}$	Ethanol	334
$\mathrm{(C_6H_5CH_2O)_2CO}$	$\mathrm{C_6H_5CH_2C(C_2H_5)(CO_2C_2H_5)_2}$	53	$\mathrm{NaOCH_2C_6H_5}$	$\mathrm{(C_6H_5CH_2O)_2CO}$	890, 330
$p\text{-}\mathrm{O_2NC_6H_4CH_2Cl}$	$p\text{-}\mathrm{O_2NC_6H_4CH_2C(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Ethanol	740
$p\text{-}\mathrm{IC_6H_4CH_2Br}$	$p\text{-}\mathrm{IC_6H_4CH_2C(C_2H_5)(CO_2C_2H_5)_2}$	64	$\mathrm{NaOC_2H_5}$	Ethanol	900
Chloromethyl cyclohexyl sulfide	Diethyl ethyl[(cyclohexylthio)methyl]-malonate	—	$\mathrm{NaOC_2H_5}$	Toluene	125, 899
C_8					
$n\text{-}\mathrm{C_8H_{17}Br}$	$n\text{-}\mathrm{C_8H_{17}C(C_2H_5)(CO_2C_2H_5)_2}$	85	Na	Ether	709
$(+)\text{-}n\text{-}\mathrm{C_6H_{13}CH(CH_3)Br}$	$(+)\text{-}n\text{-}\mathrm{C_6H_{13}CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2}$	41	$\mathrm{NaOC_2H_5}$	Ethanol	901
$(-)\text{-}n\text{-}\mathrm{C_6H_{13}CH(CH_3)Br}$	$(-)\text{-}n\text{-}\mathrm{C_6H_{13}CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2}$	41	$\mathrm{NaOC_2H_5}$	Ethanol	901
$(+-)\text{-}n\text{-}\mathrm{C_6H_{13}CH(CH_3)Br}$	$(+-)\text{-}n\text{-}\mathrm{C_6H_{13}CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2}$	43	$\mathrm{NaOC_2H_5}$	Ethanol	901
$n\text{-}\mathrm{C_3H_7CH(CH_3)(CH_2)_3Br}$	$n\text{-}\mathrm{C_3H_7CH(CH_3)(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Ethanol	550
$n\text{-}\mathrm{C_3H_7CH(C_2H_5)CH_2Br}$	$n\text{-}\mathrm{C_3H_7CH(C_2H_5)CH_2C(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Ethanol	550
$\mathrm{C_2H_5CH(CH_3)CH_2CH(CH_3)CH_2Br}$	$\mathrm{C_2H_5CH(CH_3)CH_2CH(CH_3)CH_2C(C_2H_5)\text{-}(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Ethanol	550
$n\text{-}\mathrm{C_4H_9O(CH_2)_2O(CH_2)_2Br}$	$n\text{-}\mathrm{C_4H_9O(CH_2)_2O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2}$	30–40	—	—	374
$\mathrm{(C_2H_5)_2CHCHS(C_2H_5)Cl}$	$\mathrm{(C_2H_5)_2CHCHS(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2}$	—	$\mathrm{NaOC_2H_5}$	Toluene	126
β-Cyclohexylethyl bromide	Diethyl ethyl-(β-cyclohexylethyl)malonate	—	$\mathrm{NaOC_2H_5}$	Ethanol	902
β-Cyclohexylideneethyl bromide	Diethyl ethyl-(β-cyclohexylideneethyl)-malonate	65	$\mathrm{NaOC_2H_5}$	$\mathrm{(C_2H_5O)_2CO}$	663

Note: References 577–1080 are on pp. 322–331.
‡ The halogen was not specified.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R' = C_2H_5 (Cont.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$C_6H_5(CH_2)_2Br$	$C_6H_5(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$	48	K	Xylene	881
$C_6H_5O(CH_2)_2Cl$	$C_6H_5O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$	—	—	—	374
$C_6H_5CH_2SCH_2Cl$	$C_6H_5CH_2SCH_2C(C_2H_5)(CO_2C_2H_5)_2$	55	Na	Ether	205
$C_6H_5CH(CH_3)X\ddagger$	$C_6H_5CH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$	—	—	—	371
$p\text{-}CH_3OC_6H_4CH_2Cl$	$n\text{-}CH_3OC_6H_4CH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	903
$C_6H_5CH_2OCH_2Cl$	$C_6H_5CH_2OCH_2C(C_2H_5)(CO_2C_2H_5)_2$	50	Na	Ether	542
$C_6H_5COCH_2Cl$	$C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	Ether	891
$C_6H_5COCH_2Cl$	$C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	C_6H_6	891
$C_6H_5COCH_2Br$	$C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	Ether	901, 894
$C_6H_5COCH_2Br$	$C_6H_5COCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	C_6H_6	894
$C_6H_5COCH_2Br$	$H_5C_6C{-}CO$ / $HC{-}{-}C(C_2H_5)CO_2C_2H_5$ / $O{-}{-}CO$	—	$NaOC_2H_5$	Ethanol	106
$H_5C_6CH{-}{-}CH_2$ (O)	$H_5C_6CHCH_2C(C_2H_5)CO_2C_2H_5$ / $O{-}{-}CO$	65	$NaOC_2H_5$	Ethanol	11
C_9					
$n\text{-}C_3H_7CH(CH(CH_3)CH(C_2H_5)CH_2Br$	$n\text{-}C_3H_7CH(CH(CH_3)CH(C_2H_5)CH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	550
$i\text{-}C_5H_{11}CH(C_2H_5)CH_2Br$	$i\text{-}C_5H_{11}CHC_2H_5CH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	550
$C_6H_5(CH_2)_3Br$	$C_6H_5(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	53	$NaOC_2H_5$	Ethanol	900
$C_6H_5O(CH_2)_3Cl$	$C_6H_5O(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	—	—	—	371
C_{10}					
δ-Cyclohexylbutyl bromide	Diethyl ethyl(δ-cyclohexylbutyl)malonate	—	$NaOC_2H_5$	Ethanol	902
5-Methoxy-2,4-dimethylbenzyl chloride-KI	Diethyl ethyl(5-methoxy-2,4-dimethylbenzyl)malonate	84	$NaOC_2H_5$	Ethanol	905

2-Phenyl-4-chloromethyl-thiazole	Diethyl ethyl-(2-phenyl-4-thiazolylmethyl)malonate	50	$NaOC_2H_5$	Ethanol	548
C_{11}					
n-$C_{11}H_{23}X$‡	n-$C_{11}H_{23}C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
1-Bromomethylnaphthalene	Diethyl ethyl-(1-naphthylmethyl)malonate	63	Na	C_6H_6	153
2-Bromomethylnaphthalene	Diethyl ethyl-(2-naphthylmethyl)malonate	—	Na	C_6H_6	153
C_{12}					
n-$C_{12}H_{25}X$‡	n-$C_{12}H_{25}C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	888
β-(p-t-Butylphenyl)ethyl-bromide	Diethyl ethyl-[β-(p-t-butylphenyl)ethyl]-malonate	60	Na	Toluene	413
1-Acenaphthenyl chloride	Diethyl ethyl-(1-acenaphthenyl)malonate	91	$NaOC_2H_5$	Ethanol	824
C_{13}–C_{16}					
n-$C_{13}H_{27}Br$	n-$C_{13}H_{27}C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
n-$C_{14}H_{29}I$	n-$C_{14}HC_{29}(C_2H_5)(CO_2C_2H_5)_2$	73	—	—	034,888
n-$C_{15}H_{31}I$	n-$C_{15}HC_{33}(C_2H_5)(CO_2C_2H_5)_2$	75	Na	Toluene	900
n-$C_{16}H_{33}I$	n-$C_{16}HC_{33}(C_2H_5)(CO_2C_2H_5)_2$	83	$NaOC_2H_5$	Ethanol	135
C_{10}–C_{16}					
n-$C_{10}H_{21}Br$ ††	$(CH_2)_2C(C(C_{10}H_{21}$-$n)CO_2C_2H_5$, O—CO	—	$NaOC_2H_5$	Ethanol	527
n-$C_{12}H_{25}Br$ ††	$(CH_2)_2C(C(C_{12}H_{25}$-$n)CO_2C_2H_5$, O—CO	—	$NaOC_2H_5$	Ethanol	527
n-$C_{13}H_{27}Br$ ††	$(CH_2)_2C(C(C_{13}H_{27}$-$n)CO_2C_2H_5$, O—CO	—	$NaOC_2H_5$	Ethanol	527
n-$C_{14}H_{29}Br$ ††	$(CH_2)_4C(C(C_{14}H_{29}$-$n)CO_2C_2H_5$, O—CO	—	$NaOC_2H_5$	Ethanol	527

Note: References 527–1080 are on pp. 322–381.

‡ The halogen was not specified.

†† The lactone $CH_2CH_2CH(CH_2CO_2C_2H_5)_2$ was used as the ester to be alkylated.

O——CO

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
†† (Cont.)	n-$C_{16}H_{33}Br$	$(CH_2)_2C(C_{16}H_{33}\text{-}n)CO_2C_2H_5$ $\mathrm{O\!-\!\!-\!\!CO}$	—	$NaOC_2H_5$	Ethanol	527
C_2H_5O	C_3–C_{11} $CH_2=CHCH_2Br$ i-$C_4H_9CH=CHCH_2Br$ $Br(CH_2)_3Br$	$CH_2=CHCH_2C(OC_2H_5)(CO_2C_2H_5)_2$ i-$C_4H_9CH=CHCH_2C(OC_2H_5)(CO_2C_2H_5)_2$ $Br(CH_2)_3C(OC_2H_5)(CO_2C_2H_5)_2$ and $(C_2H_5O)_2C(OC_2H_5)(CH_2)_3$- $C(OC_2H_5)(CO_2C_2H_5)_2$	— — —	$NaOC_2H_5$ $NaOC_2H_5$ $NaOC_2H_5$	Ethanol Ethanol Toluene-ethanol	907 907 903
	$Br(CH_2)_4Br$	$Br(CH_2)_4C(OC_2H_5)(CO_2C_2H_5)_2$ and $(C_2H_5O_2)C(OC_2H_5)(CH_2)_4$- $C(OC_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene-ethanol	903
	$C_2H_5CH=CHCH_2Br$ $Br(CH_2)_{10}Br$	$C_2H_5CH=CHCH_2C(OC_2H_5)(CO_2C_2H_5)_2$ $Br(CH_2)_{10}C(OC_2H_5)(CO_2C_2H_5)_2$ and $(C_2H_5O_2)C(OC_2H_5)(CH_2)_{10}C(OC_2H_5)$- $(CO_2C_2H_5)_2$	— —	$NaOC_2H_5$ $NaOC_2H_5$	Ethanol Toluene-ethanol	907 903
	$CH_2=CH(CH_2)_9Br$ CH_3I	$CH_2=CH(CH_2)_9C(OC_2H_5)(CO_2C_2H_5)_2$ $(C_2H_5O_2)C(OC_2H_5)CH_3C(CH_3)(CO_2C_2H_5)_2$	— 50	$NaOC_2H_5$ $NaOC_2H_5$	Ethanol Ethanol	907 204
CH_3OCH_2	C_1 CH_3I $CHCl_3$	n-$C_3H_7C(CH_3)(CO_2C_2H_5)_2$ $Cl_2ClC(C_3H_7\text{-}n)(CO_2C_2H_5)_2$ and $(C_2H_5O_2)C(C_3H_7\text{-}n)CHCl\text{-}$ $C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	— —	$NaOC_2H_5$ Na	Ethanol Ether	613 231
††	C_2 $Br(CH_2)_2Br$	$(CH_2)_2C(C_3H_7\text{-}n)CO_2C_2H_5$ $\mathrm{O\!-\!\!-\!\!CO}$	—	Na	C_6H_6	555
n-C_3H_7	$Br(CH_2)_2Br$	$Br(CH_2)_2C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	172

Halide	Product	Yield %	NaOC₂H₅	Solvent	Reference
CH₂—CH₂ \ / O	(CH₂)₂CH(C₃H₇-n) | —CO / O—CO	70	NaOC₂H₅	Ethanol	282
C₃					
C₂H₅SCH₂Cl	C₂H₅SCH₂C(C₃H₇-n)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
CH₃SCH(CH₃)Cl	CH₃SCH(CH₃)C(C₃H₇-n)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	126
Br(CH₂)₃Br	Br(CH₂)₃C(C₃H₇-n)(CO₂C₂H₅)₂	45	Na	—	656
C₄					
C₂H₅CH(CH₃)Br	C₂H₅CH(CH₃)C(C₃H₇-n)(CO₂C₂H₅)₂	53	NaOC₂H₅	Ethanol	909, 547
C₂H₅O(CH₂)₂Br	C₂H₅O(CH₂)₂C(C₃H₇-n)(CO₂C₂H₅)₂	43	NaOC₂H₅	Ethanol	910
C₂H₅OCH(CH₃)Cl	C₂H₅OCH(CH₃)C(C₃H₇-n)(CO₂C₂H₅)₂	66	NaNH₂	C₆H₆-ether	203
CH₂=CHO(CH₂)₂Cl	CH₂=CHO(CH₂)₂C(C₃H₇-n)(CO₂C₂H₅)₂	40–50	NaOC₂H₅	Ethanol	541
C₂H₅SCH(CH₃)Cl	C₂H₅SCH(CH₃)C(C₃H₇-n)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	126
ClCH₂CO₂C₂H₅	C₂H₅O₂CCH₂C(C₃H₇-n)(CO₂C₂H₅)₂	—	Na	Ether	653
ClCH₂CO₂C₂H₅	C₂H₅O₂CCH₂C(C₃H₇-n)(CO₂C₂H₅)₂	—	Na	C₆H₆	653
C₅					
n-C₅H₁₁Br	n-C₅H₁₁C(C₃H₇-n)(CO₂C₂H₅)₂	73	NaOC₂H₅	(C₂H₅O)₂CO	44
n-C₄H₉SCH₂Cl	n-C₄H₉SCH₂C(C₃H₇-n)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
C₂H₅CH(CH₃)CH₂Br	C₂H₅CH(CH₃)CH₂C(C₃H₇-n)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	551
i-C₅H₁₁Br	i-C₅H₁₁C(C₃H₇-n)(CO₂C₂H₅)₂	41	NaOC₂H₅	Ethanol	718, 748
i-C₄H₉SCH(CH₃)Cl	i-C₄H₉SCH(CH₃)C(C₃H₇-n)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	120
CH₃CHBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)C(C₃H₇-n)(CO₂C₂H₅)₂	25	NaOC₂H₅	Ethanol	223
Cyclopentyl halide‡	Diethyl cyclopentyl-(n-propyl)malonate	—		—	911
C₆					
n-C₆H₉SCH(CH₃)Cl	n-C₆H₉SCH(CH₃)C(C₃H₇-n)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	126
C₂H₅CHBrCO₂C₂H₅	C₂H₅O₂CCH(C₂H₅)C(C₃H₇-n)(CO₂C₂H₅)₂	12	NaOC₂H₅	Ethanol	223
(CH₃)₂CBrCO₂C₂H₅	C₂H₅O₂CC(CH₃)₂C(C₃H₇-n)(CO₂C₂H₅)₂	21	NaOC₂H₅	Ethanol	223
2,4-Dinitrochlorobenzene	Diethyl n-propyl-(2,4-dinitrophenyl)-malonate	54	Na	Ether	139

Note: References 517–1050 are on pp. 322–331.

‡ The halogen was not specified.

†† The lactone CH₂CH₂CH(CO)₂C₃H₅ | O—CO was used as the ester to be alkylated.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$n\text{-}C_3H_7$ (*Cont.*)						
	C_7					
	$i\text{-}C_3H_7CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_3H_7\text{-}i)C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	Poor	$NaOC_2H_5$	Ethanol	223
	β-Cyclopentylethyl bromide	Diethyl n-propyl-(β-cyclopentylethyl)-malonate	50–60	$NaOC_2H_5$	Ethanol	725
	C_8					
	β-Cyclohexylethyl bromide	Diethyl n-propyl-(β-cyclohexylethyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	$C_6H_5O(CH_2)_2Br$	$C_6H_5O(CH_2)_2C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	48	$NaOC_2H_5$	Ethanol	910
	C_9					
	γ-Cyclohexylpropyl bromide	Diethyl n-propyl-(γ-cyclohexylpropyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	$C_6H_5O(CH_2)_3Cl$	$C_6H_5O(CH_2)_3C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	27	$NaOC_3H_7\text{-}n$	$n\text{-}C_3H_7OH$	771
	C_{10}					
	$n\text{-}C_{10}H_{21}X\ddagger$	$n\text{-}C_{10}H_{21}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	δ-Cyclohexylbutyl bromide	Diethyl n-propyl-(δ-cyclohexylbutyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	$C_{11}\text{-}C_{16}$					
	$n\text{-}C_{11}H_{23}X\ddagger$	$n\text{-}C_{11}H_{23}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	$n\text{-}C_{12}H_{25}X\ddagger$	$n\text{-}C_{12}H_{25}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	β-(1-Naphthyl)ethyl bromide	Diethyl n-propyl-[β-(1-naphthyl)ethyl]-malonate	29	K	C_6H_6	419
	$n\text{-}C_{13}H_{27}X\ddagger$	$n\text{-}C_{13}H_{27}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	$n\text{-}C_{14}H_{29}X\ddagger$	$n\text{-}C_{14}H_{29}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	$n\text{-}C_{16}H_{33}I$	$n\text{-}C_{16}H_{33}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Ethanol	135
$Cl(CH_2)_3$	None	Diethyl cyclobutane-1,1-dicarboxylate	88	$NaOC_2H_5$	Ethanol	622,480,490
$Br(CH_2)_3$	None	Diethyl cyclobutane-1,1-dicarboxylate	74	$NaOC_2H_5$	Ethanol	315

	Halide	Product	Yield (%)	Condensing Agent	Solvent	Reference
$I(CH_2)_3$	None	Diethyl cyclobutane-1,1-dicarboxylate	—	$Na(C_6H_5CHCN)$	Ether	92
	None	Diethyl cyclobutane-1,1-dicarboxylate	—	$Na[C_6H_5\text{-}C(CO_2C_2H_5)_2]$	Toluene	92
††	$n\text{-}C_{14}H_{29}Br$	$CH_3CHCH_2C(C_{14}H_{29}\text{-}n)CO_2C_2H_5$ (O——CO lactone)	—	$NaOC_2H_5$	Ethanol	527
††	$n\text{-}C_{16}H_{33}Br$	$CH_3CHCH_2C(C_{16}H_{33}\text{-}n)CO_2C_2H_5$ (O——CO lactone)	—	$NaOC_2H_5$	Ethanol	527
$i\text{-}C_3H_7$						
	C_1					
	CH_3I	$i\text{-}C_3H_7C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	509
	C_2					
	$C_2H_5X\ddagger$	$i\text{-}C_3H_7C(C_2H_5)(CO_2C_2H_5)_2$	Very low	$NaOC_2H_5$	Ethanol	145
	$C_2H_5X\ddagger$	$i\text{-}C_3H_7C(C_2H_5)(CO_2C_2H_5)_2$	10	$NaOC_2H_5$	$(C_2H_5O)_2CO$	890
	$C_2H_5X\ddagger$	$i\text{-}C_3H_7C(C_2H_5)(CO_2C_2H_5)_2$	65	$NaOC_4H_9\text{-}i$	$i\text{-}C_4H_9OH$	35
	CH_3OCH_2Cl	$CH_3OCH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	—	Na	Ether	204
	$Br(CH_2)_2Br$	$Br(CH_2)_3C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	172
	C_3					
	$n\text{-}C_3H_7Br$	$n\text{-}C_3H_7C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	ca. 80	$NaOC_2H_5$	Ethanol	538
	$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	33	Na	Ether	205
	$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$i\text{-}C_3H_7I$	$(i\text{-}C_3H_7)_2C(CO_2C_2H_5)_2$	40	Na	Ether	52
	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44
	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	90	$Mg(OC_2H_5)_2$	Ethanol	56
	C_4					
	$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	ca. 80	$NaOC_2H_5$	Ethanol	536, 770
	$C_2H_5CH(CH_3)Br$	$C_2H_5CH(CH_3)C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	26	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44
	$i\text{-}C_4H_9Br$	$i\text{-}C_4H_9C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	67	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44
	$i\text{-}C_3H_7SCH_2Cl$	$i\text{-}C_3H_7SCH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125

Note: References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

†† The lactone $CH_3CHCH_2CHCO_2C_2H_5$ (O——CO) was used as the ester to be alkylated.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$n\text{-}C_3H_7$ (Cont.)						
	C_7					
	$i\text{-}C_5H_{11}CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_3H_7\text{-}i)C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	Poor	$NaOC_2H_5$	Ethanol	223
	β-Cyclopentylethyl bromide	Diethyl n-propyl-(β-cyclopentylethyl)-malonate	50–60	$NaOC_2H_5$	Ethanol	725
	C_8					
	β-Cyclohexylethyl bromide	Diethyl n-propyl-(β-cyclohexylethyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	$C_6H_5O(CH_2)_2Br$	$C_6H_5O(CH_2)_2C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	48	$NaOC_2H_5$	Ethanol	910
	C_9					
	γ-Cyclohexylpropyl bromide	Diethyl n-propyl-(γ-cyclohexylpropyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	$C_6H_5O(CH_2)_3Cl$	$C_6H_5O(CH_2)_3C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	27	$NaOC_3H_7\text{-}n$	$n\text{-}C_3H_7OH$	774
	C_{10}					
	$n\text{-}C_{10}H_{21}X\ddagger$	$n\text{-}C_{10}H_{21}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	δ-Cyclohexylbutyl bromide	Diethyl n-propyl-(δ-cyclohexylbutyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	$C_{11}\text{-}C_{16}$					
	$n\text{-}C_{11}H_{23}X\ddagger$	$n\text{-}C_{11}H_{23}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	888
	$n\text{-}C_{12}H_{25}X\ddagger$	$n\text{-}C_{12}H_{25}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	β-(1-Naphthyl)ethyl bromide	Diethyl n-propyl-[β-(1-naphthyl)ethyl]-malonate	29	K	C_6H_6	419
	$n\text{-}C_{13}H_{27}X\ddagger$	$n\text{-}C_{13}H_{27}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	888
	$n\text{-}C_{14}H_{29}X\ddagger$	$n\text{-}C_{14}H_{29}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	$n\text{-}C_{16}H_{33}I$	$n\text{-}C_{16}H_{33}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Ethanol	135
$Cl(CH_2)_3$	None	Diethyl cyclobutane-1,1-dicarboxylate	88	$NaOC_2H_5$	Ethanol	622, 189, 490
$Br(CH_2)_3$	None	Diethyl cyclobutane-1,1-dicarboxylate	74	$NaOC_2H_5$	Ethanol	315

$CH_2=CHCH_2$ ($= C_3H_5$)

Halide	Product	Yield (%)	Base	Solvent	Reference
C_2					
C_2H_5Br	$C_2H_5C(C_3H_5)(CO_2C_2H_5)_2$	70–85	$NaOC_2H_5$	Ethanol	545
$Br(CH_2)_2Br$	$Br(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	172
$BrCH=CHBr$	$BrCH=CHC(C_3H_5)(CO_2C_2H_5)_2$	20	$NaNH_2$	Ether-ethanol	277
$CH_2\!-\!CH_2$ (O)	$(CH_2)_2CH(C_3H_5)$ (O—CO)	ca. 70	$NaOC_2H_5$	Ethanol	282
C_3					
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_3H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$i\text{-}C_3H_7Br$	$i\text{-}C_3H_7C(C_3H_5)(CO_2C_2H_5)_2$	40	$NaOC_2H_5$	Ethanol	531
$CH_3SCH(CH_3)Cl$	$CH_3SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	120
$CH_2=CHCH_2Br$	$(C_3H_5)_2C(CO_2C_2H_5)_2$	—	Na	Ethanol	015
$(CH_3)_2CClNO_2$	$(CH_3)_2C(NO_2)C(C_3H_5)(CO_2C_2H_5)_2$	40	Na	Ether	556
C_4					
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(C_3H_5)(CO_2C_2H_5)_2$	87	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44, 51
$C_2H_5OCH(CH_3)Cl$	$C_2H_5OCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	83	$NaNH_2$	C_6H_6-ether	203
$n\text{-}C_3H_7SCH_2Cl$	$n\text{-}C_3H_7SCH_2C(C_3H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$C_2H_5S(CH_2)_2Cl$	$C_2H_5S(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	553
$C_2H_5SCH(CH_3)Cl$	$C_2H_5SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	120
Cyclobutylmethyl tosylate	Diethyl allyl(cyclobutylmethyl)malonate	80	$NaOC_2H_5$	Ethanol	334
$CH_3CCl=CHCH_2Cl$	$CH_3CCl=CHCH_2C(C_3H_5)(CO_2C_2H_5)_2$	—	—	—	561
$CH_2=CHCH_2$ (O—CH₂)	$CH_2=CHCH_2C(C_3H_5)CO_2C_2H_5$ (O—CO)	54	$NaOC_2H_5$	Ethanol	11
C_5					
$n\text{-}C_4H_9SCH_2Cl$	$n\text{-}C_4H_9SCH_2C(C_3H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$n\text{-}C_3H_7S(CH_2)_2Cl$	$n\text{-}C_3H_7S(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	553
$n\text{-}C_3H_7CH(CH_3)Br$	$n\text{-}C_3H_7CH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	017
$C_2H_5SCH_2CH(CH_3)Cl$	$C_2H_5SCH_2CH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	70–75	$NaOC_2H_5$	Toluene	554
$n\text{-}C_3H_7OCH(CH_3)Cl$	$n\text{-}C_3H_7OCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	82	$NaNH_2$	C_6H_6-ether	203
$i\text{-}C_3H_7SCH(CH_3)Cl$	$i\text{-}C_3H_7S(CH_2)_2C(C_3H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	126
$CH_2=CHCH_2SCH(CH_3)Cl$	$CH_2=CHCH_2SCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	553
$(CH_3)_2C=CHCH_2Br$	$(CH_3)_2C=CHCH_2C(C_3H_5)(CO_2C_2H_5)_2$	Poor	$NaOC_2H_5$	Ethanol	126
$CH_3CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(CH_3)C(C_3H_5)(CO_2C_2H_5)_2$	20	$NaOC_2H_5$	Ethanol	912
2-Chloromethylthiophene	Diethyl (2-thenylallyl)malonate	65	$NaOC_2H_5$	Ethanol	223, 913

Note: References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

$$R'CH(CO_2R)_2$$

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
i-C₃H₇ (Cont.)						
	C₅					
	n-C₅H₁₁Br	n-C₅H₁₁C(C₃H₇-i)(CO₂C₂H₅)₂	70–85	NaOC₂H₅	Ethanol	515
	n-C₄H₉SCH₂Cl	n-C₄H₉SCH₂C(C₃H₇-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	i-C₃H₇C(C₂H₇-i)Br	i-C₃H₇C(C₃H₇-i)(CO₂C₂H₅)₂	ca. 50	NaOC₂H₅	Ethanol	536
	(CH₃)₂C=CHCH₂Br	(CH₃)₂C=CHCH₂C(C₃H₇-i)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	912
	(CH₃)₂C=CHCH₂Br	(CH₃)₂C=CHCH₂C(C₃H₇-i)(CO₂C₂H₅)₂	73	NaOC₂H₅	(C₂H₅O)₂CO	47
	CH₂ClBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)C(C₃H₇-i)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	253
	I(CH₂)₃CO₂C₂H₅	C₂H₅O₂C(CH₂)₃C(C₃H₇-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	672
	2-Chloromethylthiophene	Diethyl isopropyl-(2-thenyl)malonate	—	Na	None	757
	C₆					
	n-C₄H₉SCH₂)₂Cl	n-C₄H₉S(CH₂)₃C(C₃H₇-i)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	553
	n-C₄H₉SCH(CH₃)Cl	n-C₄H₉SCH(CH₃)C(C₃H₇-i)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	125
	C₂H₅CHBrCO₂C₂H₅	C₂H₅O₂CCH(C₂H₅)C(C₃H₇-i)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	223
	(CH₂)₂CBrCO₂C₂H₅	C₂H₅O₂C(C(CH₃)₂)C(C₃H₇-i)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	223
	C₇					
	i-C₃H₇CHBrCO₂C₂H₅	None	—	NaOC₂H₅	Ethanol	221
	C₆H₅CH₂Cl	C₆H₅CH₂C(C₃H₇-i)(CO₂C₂H₅)₂	45	NaOC₂H₅	(C₂H₅O)₂CO	45
	C₈–C₁₃					
	C₆H₅COCH₂Br		—	NaOC₂H₅	Ethanol	108
	2,5-Dimethylbenzyl chloride	Diethyl isopropyl-(2,5-dimethylbenzyl)-malonate	67	Na	Xylene	133
	n-C₁₃H₂₇X‡	n-C₁₃H₂₇C(C₃H₇-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	583

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
CH₂=CHCH₂ (Cont.)						
	C_6					
	n-C₄H₉S(CH₂)₃Cl	n-C₄H₉S(CH₂)₃C(C₃H₅)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	553
	n-C₄H₉SCH(CH₃)Cl	n-C₄H₉SCH(CH₃)C(C₃H₅)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	126
	i-C₄H₉SCH(CH₃)Cl	i-C₄H₉SCH(CH₃)C(C₃H₅)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	126
	CH₂=C(CH₃)CHCl	CH₂=C(CH₃)CH(C₂H₅)C(C₃H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	808
	Br(CH₂)₃CO₂C₂H₅	C₂H₅O₂C(CH₂)₃C(C₃H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	530
	(CH₃)₂CBrCO₂C₂H₅	C₂H₅O₂CC(CH₃)₂C(C₃H₅)(CO₂C₂H₅)₂	16	NaOC₂H₅	Ethanol	223
	C_7					
	n-C₄H₉SCH₂CH(CH₃)Cl	n-C₄H₉SCH₂CH(CH₃)C(C₃H₅)(CO₂C₂H₅)₂	70–75	NaOC₂H₅	Toluene	554
	i-C₃H₇CHBrCO₂C₂H₅	C₂H₅O₂CCH(C₃H₇-i)C(C₃H₅)(CO₂C₂H₅)₂	5	NaOC₂H₅	Ethanol	223
	C₆H₅CH₂Cl	C₆H₅CH₂C(C₃H₅)(CO₂C₂H₅)₂	—	—	—	506
	C_8					
	n-C₄H₉CH(C₂H₅)CH₂Br	n-C₄H₉CH(C₂H₅)CH₂C(C₃H₅)(CO₂C₂H₅)₂	—	Na	Xylene	914
	β-Cyclohexylethyl bromide	Diethyl allyl-(β-cyclohexylethyl)malonate	—	NaOC₂H₅	Ethanol	902
	o-Methylbenzyl bromide	Diethyl allyl-(o-methylbenzyl)malonate	34	NaOC₂H₅	Ethanol	516
	H₅C₆CH——CH₂ (O)	H₅C₆CHCH₂C(C₃H₅)CO₂C₂H₅ , O——CO	25	NaOC₂H₅	Ethanol	11
	C_9					
	n-C₉H₁₉Br	n-C₉H₁₉C(C₃H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	920
	γ-Cyclohexylpropyl bromide	Diethyl allyl-(γ-cyclohexylpropyl)malonate	—	NaOC₂H₅	Ethanol	902
	C_{10}–C_{12}					
	n-C₁₀H₂₁Br	n-C₁₀H₂₁C(C₃H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	920
	δ-Cyclohexylbutyl bromide	Diethyl allyl-(δ-cyclohexylbutyl)malonate	—	NaOC₂H₅	Ethanol	902
	p-i-C₃H₇C₆H₄CH₂Cl	p-i-C₃H₇C₆H₄CH₂C(C₃H₅)(CO₂C₂H₅)₂	80	NaOC₂H₅	Toluene	509
	n-C₁₁H₂₃Br	n-C₁₁H₂₃C(C₃H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	920

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$n\text{-}C_4H_9$ (Cont.)	C_3					
	$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125, 893
	C_3H_7Br	$n\text{-}C_3H_7C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	915
	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	148
	$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	47	Na	None	656, 129
	$(CH_3)_2CCNO_2$	$(CH_3)_2C(NO_2)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	39	Na	Ether	550
	C_4					
	$n\text{-}C_4H_9Br$	$(n\text{-}C_4H_9)_2C(CO_2C_2H_5)_2$	74	$NaOC_2H_5$	Ethanol	142
	$n\text{-}C_4H_9I$	$(n\text{-}C_4H_9)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	141
	$sec\text{-}C_4H_9Br$	$sec\text{-}C_4H_9C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	08	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44
	$C_2H_5OCH(CH_2)_2Cl$	$C_2H_5OCH(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70	$NaNH_2$	C_6H_6-ether	203
	$CH_2=CHOCH(CH_2)_2Cl$	$CH_2=CHOCH(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	40–50	$NaOC_2H_5$	Ethanol	541
	$C_2H_5SCHCH_2Cl$	$C_2H_5SCH(CH_2)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	126
	$C_2H_5OCH(CH_2)Cl$	$C_2H_5OCH(CH_2)Cl(C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	68	Na	Ether	277
	$C_2H_5OCHBrCH_2Br$	$CH_3CH(OC_2H_5)C(C_4H_9\text{-}n)CO_2C_2H_5$	56	Na	Ether	277
	$CH_3CCl=CHCH_2Cl$	$CH_3CCl=CHCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	916, 917
	$CH_2=CHCH$—CH_2	$CH_2=CHCHCH_2C(C_4H_9\text{-}n)CO_2C_2H_5$	30	$NaOC_2H_5$	Ethanol	11
	C_5					
	$n\text{-}C_5H_{11}SCH_2Cl$	$n\text{-}C_5H_{11}SCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$C_2H_5CH(C_3H_7)Br$	$C_2H_5CH(C_3H_7)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70–85	$NaOC_2H_5$	Ethanol	545
	$C_2H_5CH(CH_3)CH_2Br$	$C_2H_5CH(CH_3)CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70–85	$NaOC_2H_5$	Ethanol	545
	$i\text{-}C_5H_{11}Br$	$i\text{-}C_5H_{11}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44
	$CH_2=CHCH_2S(CH_2)_3Cl$	$CH_2=CHCH_2S(CH_2)_3C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	553
	Cyclopentyl halide	Diethyl cyclopentyl-α-butylmalonate	—	—	—	911

2-Chloromethylthiophene	Diethyl n-butyl-(2-thenyl)malonate	—	Na	None	897
$(CH_3)_2C(CH_2Br)_2$	$n\text{-}C_4H_9C(CO_2C_2H_5)_2CH_2C(CH_3)_2\text{-}$ $CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	13	NaOC$_2$H$_5$	Ethanol	918
C_6–C_7					
n-C$_6$H$_{13}$Br	$n\text{-}C_6H_{13}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	NaOC$_2$H$_5$	Ethano	641, 919
n-C$_7$H$_{15}$Br	$n\text{-}C_7H_{15}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	NaOC$_2$H$_5$	Ethanol	641
n-C$_7$H$_{15}$I	$n\text{-}C_7H_{15}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	90	NaOC$_2$H$_5$	Ethanol	399
β-Cyclopentylethyl bromide	Diethyl n-butyl-(β-cyclopentylethyl)-malonate	50–60	NaOC$_2$H$_5$	Ethanol	725
C$_6$H$_5$CH$_2$Cl	$C_6H_5CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70	NaOC$_2$H$_5$	Ethanol	121, 142, 143
p-IC$_6$H$_4$CH$_2$Br	$p\text{-}IC_6H_4CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	67	NaOC$_2$H$_5$	Ethanol	900
C_8–C_{10}					
n-C$_6$H$_{13}$CH(CH$_3$)Br	$n\text{-}C_6H_{13}CH(CH_3)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70–85	NaOC$_2$H$_5$	Ethanol	545
β-Cyclohexylethyl bromide	Diethyl n-butyl-(β-cyclohexylethyl)-malonate	—	NaOC$_2$H$_5$	Ethanol	902
C$_6$H$_5$(CH$_2$)$_2$Br	$C_6H_5(CH_2)_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	44	NaOC$_2$H$_5$	Ethanol	142
H$_5$C$_6$CH—CH$_2$ (O)	$H_5C_6CHCH_2C(C_4H_9\text{-}n)CO_2C_2H_5$ O——CO	50	NaOC$_2$H$_5$	Ethanol	11
n-C$_9$H$_{19}$X‡	$n\text{-}C_9H_{19}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	NaOC$_2$H$_5$	Ethanol	887
γ-Cyclohexylpropyl bromide	Diethyl n-butyl-(γ-cyclohexylpropyl)-malonate	—	NaOC$_2$H$_5$	Ethanol	902
C$_6$H$_5$(CH$_2$)$_3$X‡	$C_6H_5(CH_2)_3C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	35	NaOC$_2$H$_5$	Ethanol	142
n-C$_{10}$H$_{21}$X‡	$n\text{-}C_{10}H_{21}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	NaOC$_2$H$_5$	Ethanol	888
δ-Cyclohexylbutyl bromide	Diethyl n-butyl-(δ-cyclohexylbutyl)-malonate	—	NaOC$_2$H$_5$	Ethanol	902
C_{11}–C_{20}					
n-C$_{11}$H$_{23}$-X‡	$n\text{-}C_{11}H_{23}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	NaOC$_2$H$_5$	Ethanol	887
Undecenyl bromide	Diethyl undecenyl-(n-butyl)malonate	—	NaOC$_2$H$_5$	Ethanol	920
n-C$_{12}$H$_{25}$I	$n\text{-}C_{12}H_{25}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	70	Na	Toluene	906, 893
n-C$_{16}$H$_{33}$I	$n\text{-}C_{16}H_{33}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	85	NaOC$_2$H$_5$	Ethanol	135
n-C$_{20}$H$_{41}$I	$n\text{-}C_{20}H_{41}C(C_4H_9\text{-}n)(CO_2H)_2$	90	NaOC$_4$H$_9$-n	n-C$_4$H$_9$OH	684
i-C$_4$H$_9$ — **C_2**					
C$_2$H$_5$Br	$i\text{-}C_4H_9C(C_2H_5)_2(CO_2C_2H_5)_2$	—	Na	None	532
C$_2$H$_5$I	$i\text{-}C_4H_9C(C_2H_5)(CO_2C_2H_5)_2$	74	NaOC$_2$H$_5$	Ethanol	057

Note: References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, R′CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R′	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
i-C₄H₉ (Cont.)	CH₃SCH₂Cl	CH₃SCH₂C(C₄H₉-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	BrCH₂CH₂Br	(CH₂)₂C((C₄H₉-i)CO₂C₂H₅	66	Na	C₆H₆	555
		O——CO / O——				
	Br(CH₂)₂Br	Br(CH₂)₂C(C₄H₉-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	172
C₃	C₂H₅SCH₂Cl	C₂H₅SCH₂C(C₄H₉-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	(CH₃)₂CClNO₂	(CH₃)₂C(NO₂)C(C₄H₉-i)(CO₂C₂H₅)₂	45	Na	Ether	550
C₄	i-C₄H₉Br	(i-C₄H₉)₂C(CO₂C₂H₅)₂	76	NaOC₂H₅	Ethanol	642
	i-C₄H₉Br	(i-C₄H₉)₂C(CO₂C₂H₅)₂	76	NaOC₂H₅	(C₂H₅O)₂CO	44
	C₂H₅SCH(CH₃)Cl	C₂H₅SCH(CH₃)C(C₄H₉-i)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	126
C₅	n-C₄H₉SCH₂Cl	n-C₄H₉SCH₂C(C₄H₉-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125, 893
	i-C₅H₁₁Br	i-C₅H₁₁C(C₄H₉-i)(CO₂C₂H₅)₂	73	NaOC₂H₅	Ethanol	657
	CH₂=CHCH₂SCH(CH₃)Cl	CH₂=CHCH₂SCH(CH₃)C(C₄H₉-i)(CO₂C₂H₅)₂	70–90	NaOC₂H₅	Toluene	126, 899
	CH₃CHBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)C(C₄H₉-i)(CO₂C₂H₅)₂	21	NaOC₂H₅	Ethanol	223
	2-Chloromethylthiophene	Diethyl i-butyl-(2-thenyl)malonate	—	Na	None	897
C₆	C₂H₅CHBrCO₂C₂H₅	C₂H₅O₂CCHC₂H₅)C(C₄H₉-i)(CO₂C₂H₅)₂	10	NaOC₂H₅	Ethanol	223
	(CH₃)₂CBrCO₂C₂H₅	C₂H₅O₂CC(CH₃)₂C(C₄H₉-i)(CO₂C₂H₅)₂	13	NaOC₂H₅	Ethanol	223
C₇–C₁₂	i-C₃H₇CHBrCO₂C₂H₅	C₂H₅O₂CCH(C₃H₇-i)C(C₄H₉-i)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	223
	n-C₁₀H₂₁X‡	n-C₁₀H₂₁C(C₄H₉-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	888

	Halide (X)	Product	Yield	Condensing agent	Solvent	Reference
$ClCH_2C(CH_3)CH_2$	$n\text{-}C_{12}H_{25}X$‡	$n\text{-}C_{12}H_{25}C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	888
	None	Diethyl 3-methylcyclobutane-1,1-dicarboxylate	83	$NaOC_2H_5$	Ethanol	482, 481
C_2						
$sec\text{-}C_4H_9$	C_2H_5Br	$C_2H_5C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	Poor	$NaOC_2H_5$	Ethanol	148
	C_2H_5Br	$C_2H_5C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	95	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44, 51
						227
	C_2H_5I	$C_2H_5C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	Poor	$NaOC_2H_5$	Ethanol	146
	$(C_2H_5O)_2CO$	$C_2H_5C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	Poor	$NaOC_2H_5$	$(C_2H_5O)_2CO$	330
	CH_3SCH_2Cl	$CH_3SCH_2C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
C_3						
	$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	86	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44, 51
	$C_2H_5OCH(CH_3)Cl$	$C_2H_5OCH(CH_3)C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	84	$NaNH_2$	C_6H_6-ether	203
C_4						
	$sec\text{-}C_4H_9Br$	$(sec\text{-}C_4H_9)_2C(CO_2C_2H_5)_2$	15	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44
	$sec\text{-}C_4H_9Br$	$(sec\text{-}C_4H_9)_2C(CO_2C_4H_9\text{-}sec)_2$§§	25 (59)§	$NaOC_4H_9\text{-}sec$	$(sec\text{-}C_4H_9O)_2CO$	44
	$(sec\text{-}C_4H_9O)_2CO$	$(sec\text{-}C_4H_9)_2C(CO_2C_4H_9\text{-}sec)_2$§§	Poor	$NaOC_4H_9\text{-}sec$	$(sec\text{-}C_4H_9O)_2CO$	330
C_5						
	$n\text{-}C_5H_{11}Br$	$n\text{-}C_5H_{11}C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44
	$n\text{-}C_4H_9SCH_2Cl$	$n\text{-}C_4H_9SCH_2C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$i\text{-}C_5H_{11}Br$	$i\text{-}C_5H_{11}C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	$(C_2H_5O)_2CO$	447
$t\text{-}C_4H_9$	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	36 (53)§	$NaOC_2H_5$	$(C_2H_5O)_2CO$	4
$CH_3CCl{=}CHCH_2$	C_2H_5X‡	$CH_3CCl{=}CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	80	—	—	561
	$CH_3CCl{=}CHCH_2Cl$	$(CH_3CCl{=}CHCH_2)_2C(CO_2C_2H_5)_2$	—	—	—	561
	$i\text{-}C_5H_{11}X$‡	$CH_3CCl{=}CHCH_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	—	—	—	561
$CH_2{=}C(CH_3)CH_2$	CH_3SCH_2Cl	$CH_2{=}C(CH_3)CH_2C(CH_2SCH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$C_2H_5SCH_2Cl$	$CH_2{=}C(CH_3)CH_2C(CH_2SC_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$n\text{-}C_3H_7X$‡	$CH_2{=}C(CH_3)CH_2C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
	$i\text{-}C_3H_7X$‡	$CH_2{=}C(CH_3)CH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552

Note: References 577–1050 are on pp. 325–331.

‡ The halogen was not specified.

§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

§§ Di-sec-butyl sec-butylmalonate was used in this experiment.

TABLE III —Continued

ALKYLATION OR MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

| R	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$CH_3 \cdot CCH_2 \cdot CH_2$	$CH_3 \cdot CHCH_2N:$	$CH_2=C(CH_3)CH_2C(CO_2C_2H_5)_2 \atop \underset{CH_2CH=CH_2}{\vert}$	—	$NaOC_2H_5$	Ethanol	552
C_5						
	$n\text{-}C_3H_7N:$	$CH_2=C(CH_3)CH_2C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
	$iso\text{-}C_3H_7N:$	$CH_2=C(CH_3)CH_2C(C_3H_7\text{-}iso)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
	$iso\text{-}C_4H_9N:$	$CH_2=C(CH_3)CH_2C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
	$CH_3 \cdot C(CH_3)_2CH_2N:$	$[CH_2=C(CH_3)CH_2]_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
C_6						
	$n\text{-}C_4H_9N:$	$CH_2=C(CH_3)CH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
	$n\text{-}C_3H_7CH(CH_3)N:$	$CH_2=C(CH_3)CH_2C(CO_2C_2H_5)_2 \atop \underset{CH(CH_3)C_3H_7\text{-}n}{\vert}$	—	$NaOC_2H_5$	Ethanol	552
	$C_2H_5CH(CH_3)CH_2N:$	$CH_3=C(CH_3)CH_2C(CO_2C_2H_5)_2 \atop \underset{CH_2CH(CH_3)C_2H_5}{\vert}$	—	$NaOC_2H_5$	Ethanol	552
	$iso\text{-}C_5H_{11}N:$	$CH_2=C(CH_3)CH_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
	$CH_2=CHCH_2SCH(CH_3)Cl$	$CH_3 \cdot C(CH_3)CH_2C(CO_2C_2H_5)_2 \atop \underset{CH_2CHSCH_2CH=CH_2}{\vert}$	70–90	$NaOC_2H_5$	Toluene	120
	2-Chloromethylthiophene	$CH_2=C(CH_3)CH_2C(CH_2C_4H_3S)(CO_2C_2H_5)_2$	—	Na	None	897
C_6						
	$n\text{-}C_6H_{13}N:$	$CH_2=C(CH_3)CH_2C(C_6H_{13}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	552
	$(C_2H_5)_2CHCH_2N:$	$CH_3=C(CH_3)CH_2C(CO_2C_2H_5)_2 \atop \underset{CH_2CH(C_2H_5)_2}{\vert}$	—	$NaOC_2H_5$	Ethanol	552

Ester	Halide	Product	%	Base	Solvent	Reference
CH₂⟍CHCH₂⟋CH₂ (=C_4H_7)	C_5–C_{14} n-$C_5H_{11}Br$	n-$C_5H_{11}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_6H_{13}Br$	n-$C_6H_{13}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_7H_{15}Br$	n-$C_7H_{15}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_8H_{17}Br$	n-$C_8H_{17}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_9H_{19}Br$	n-$C_9H_{19}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_{10}H_{21}Br$	n-$C_{10}H_{21}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_{11}H_{23}Br$	n-$C_{11}H_{23}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_{12}H_{25}Br$	n-$C_{12}H_{25}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
	n-$C_{14}H_{29}Br$	n-$C_{14}H_{29}C(C_4H_7)(CO_2C_2H_5)_2$	60–66	$NaOC_2H_5$	Ethanol	619
$C_2H_5O_2CCH_2$	C_1–C_7 CH_3I	$C_2H_5O_2CCH_2C(CH_3)(CO_2C_2H_5)_2$	—	Na	None	101
	C_2H_5I	$C_2H_5O_2CCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	None	101
	n-$C_5H_{11}I$	$C_2H_5O_2CCH_2C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	921
	$ClCH_2CO_2C_2H_5$	$(C_2H_5O_2CCH_2)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	922
	$C_6H_5CH_2Cl$	$C_2H_5O_2CCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	—	Na	None	923
2-Thienyl (=C_7H_5S)	C_2H_5I	Dimethyl ethyl-(2-furyl)malonate*	88	$NaOCH_3$	Methanol	379
	n-C_3H_7Br	n-$C_3H_7C(C_4H_3S)(CO_2C_2H_5)_2$	74	$NaOC_2H_5$	$(C_2H_5O)_2CO$	924
	CH_2=$CHCH_2Br$	CH_2=$CHCH_2C(C_4H_3S)(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Ethanol	924
	i-C_4H_9Br	n-$C_4H_9C(C_4H_3S)(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	$(C_2H_5O)_2CO$	924
	CH_2=$C(CH_3)CH_2Cl$	i-$C_4H_9C(C_4H_3S)(CO_2C_2H_5)_2$	37	$NaOC_2H_5$	$(C_2H_5O)_2CO$	924
	n-$C_5H_{11}I$	CH_2=$C(CH_3)CH_2C(C_4H_3S)(CO_2C_2H_5)_2$	53	$NaOC_2H_5$	Ethanol	924
	Cyclopentyl bromide	n-$C_5H_{11}C(C_4H_3S)C(C_4H_3S)(CO_2C_2H_5)_2$	77	$NaOC_2H_5$	$(C_2H_5O)_2CO$	924
	2-Cyclopentenyl chloride	Diethyl cyclopentyl-(2-thienyl)malonate	66	$NaOC_2H_5$	$(C_2H_5O)_2CO$	924
	2-Chloromethylthiophene	Diethyl 2-cyclopentenyl-(2-thienyl)malonate	76	$NaOC_2H_5$	Ethanol	924
		Diethyl 2-thienyl-(2-thienyl)malonate	—	$NaOC_2H_5$	Ethanol	50
	n-$C_6H_{13}Br$	n-$C_6H_{13}C(C_4H_3S)(CO_2C_2H_5)_2$	74	$NaOC_2H_5$	$(C_2H_5O)_2CO$	924
	Cyclohexyl bromide	Diethyl cyclohexyl-(2-thienyl)malonate	51	$NaOC_2H_5$	$(C_2H_5O)_2CO$	924
	2-Cyclohexenyl bromide	Diethyl 2-cyclohexenyl-(2-thienyl)malonate	82	$NaOC_2H_5$	Ethanol	924

Note: References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

‡ The halogen was not specified.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_3						
$n\text{-}C_5H_{11}$						
	C_2					
	C_2H_5Br	$n\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	40	$NaOC_2H_5$	Ethanol	148
	$BrCH_2CH_2Br$	$(CH_2)_2C(C_5H_{11}\text{-}n)CO_2C_2H_5$ $\begin{array}{c}\|\quad\quad\|\\ O\!-\!CO\end{array}$	—	Na	C_6H_6	555
	C_3					
	$CH_3SCH(CH_3)Cl$	$CH_3SCH(CH_3)C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	126
	$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	70–85	$NaOC_2H_5$	Ethanol	545, 743
	$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	Na	—	656
	C_4					
	$C_2H_5SCH(CH_3)Cl$	$C_2H_5SCH(CH_3)C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	126
	$i\text{-}C_4H_9Br$	$n\text{-}C_5H_{11}C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	70–85	$NaOC_2H_5$	Ethanol	545
	$C_5\text{-}C_7$					
	$n\text{-}C_5H_{11}Br$	$(C_5H_{11}\text{-}n)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	641
	$n\text{-}C_6H_{13}Br$	$n\text{-}C_6H_{13}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	641
	$n\text{-}C_7H_{15}Br$	$n\text{-}C_7H_{15}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	641
	$CH_3CHBr(CH_2)_2CO_2C_2H_5$	None	—	$NaOC_2H_5$	Ethanol	720
	$C_8\text{-}C_{16}$					
	$n\text{-}C_8H_{17}X\ddagger$	$n\text{-}C_8H_{17}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	β-Cyclohexylethyl bromide	Diethyl n-amyl-(β-cyclohexylethyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	γ-Cyclohexylpropyl bromide	Diethyl n-amyl-(γ-cyclohexylpropyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	$n\text{-}C_9H_{19}Br$	$n\text{-}C_9H_{19}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	888
	δ-Cyclohexylbutyl bromide	Diethyl n-amyl-(δ-cyclohexylbutyl)-malonate	—	$NaOC_2H_5$	Ethanol	902

	Reagent	Product		Base	Solvent	Reference
C_{11}	$n\text{-}C_{10}H_{21}X\ddagger$	$n\text{-}C_{10}H_{21}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	$n\text{-}C_{11}H_{23}X\ddagger$	$n\text{-}C_{11}H_{23}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	888
	$n\text{-}$Undecenyl bromide	Diethyl n-amyl-(n-undecenyl)malonate	—	$NaOC_2H_5$	Ethanol	920
	$n\text{-}C_{12}H_{25}X\ddagger$	$n\text{-}C_{12}H_{25}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
	$n\text{-}C_{16}H_{33}I$	$n\text{-}C_{16}H_{33}C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	81	$NaOC_2H_5$	Ethanol	135
C_2	C_2H_5Br	$i\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	86	$NaOC_2H_5$	Ethanol	532
	$C_2H_5X\ddagger$	$i\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	78	$NaOC_4H_9\text{-}t$	$t\text{-}C_4H_9OH$	35
	$(C_2H_5O)_2CO$	$i\text{-}C_5H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	45 (00)§	$NaOC_2H_5$	$(C_2H_5O)_2CO$	890
	$ClC(CH_2)_2I$	$Cl(CH_2)_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	—	Na	C_6H_6	316
	$Br(CH_2)_2Br$	$(CH_2)_2C(C_5H_{11}\text{-}i)CO_2C_2H_5$ $O\!-\!\!-\!CO$	85–90	Na	C_6H_6	555, 316
	$Br(CH_2)_2Br$	$Br(CH_2)_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	172
	$BrCH\!=\!CHBr$	$BrCH\!=\!CHC(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	33	$NaNH_2$	Ether-ethanol	277
	$\overset{CH_2\!-\!CH_2}{\underset{O}{}}$	$(CH_2)_2CH(C_5H_{11}\text{-}i)$ $O\!-\!\!-\!CO$	ca. 70	$NaOC_2H_5$	Ethanol	282
C_3	$n\text{-}C_3H_7Br$	$i\text{-}C_5H_{11}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	718
	$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
	$(CH_3)_2CClNO_2$	$(CH_3)_2C(NO_2)C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	48	Na	Ether	556
	$HC\!\equiv\!CCH_2Br$	$HC\!\equiv\!CCH_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	547
	$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	43	Na	C_6H_6	537
C_4	$C_2H_5S(CH_2)_2Cl$	$C_2H_5S(CH_2)_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	553
	$C_2H_5OCH(CH_3)Cl$	$C_2H_5OCH(CH_3)C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	63	$NaNH_2$	C_6H_6-ether	203
	$i\text{-}C_4H_9Br$	$i\text{-}C_5H_{11}C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	70–85	$NaOC_2H_5$	Ethanol	545
	$CH_3CCl\!=\!CHCH_2Br$	$CH_3CCl\!=\!CHCH_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	916
	$CH_2\!=\!CHCH\!-\!CH_2$ (epoxide, O)	$CH_2\!=\!CHCH_2CH_2C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	72	$NaOC_2H_5$	Ethanol	11

Note: References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

TABLE III—Continued

ALKYLATIONS OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R	Halide used	Product	Yield %	Base	Solvent	Reference
$C_6H_5CH_2C_6H_4$(cont.)						
	$C_6H_5CHBrC_6H_5$	$C_6H_5O_2CCH(C_6H_{4-o})CH(C_6H_5)CO_2C_2H_5$	24	NaOC₂H₅	Ethanol	223
	2-$(CH_2=CHCH_2)C_6H_4$	$C_6H_5CH_2C(C_6H_{4-o})CH(CO_2C_2H_5)_2$	9	Na	None	897
	$C_6H_5CHBrCO_2C_2H_5$	$C_6H_5O_2CCH(C_6H_{4-o})CH(CO_2C_2H_5)_2$		NaOC₂H₅	Ethanol	223
	$C_6H_5CHBrCO_2C_2H_5$	$C_6H_5O_2CCH(C_6H_{4-o})CH(CO_2C_2H_5)_2$	11	NaOC₂H₅	Ethanol	223
	$C_6H_5CHBrCO_2C_2H_5$	$C_6H_5O_2CCH(C_6H_{4-o})CH(CO_2C_2H_5)_2$	Poor	NaOC₂H₅	Ethanol	223
	H_2C=CH—CH_2	H_2C=CHCH₂C(C₃H₆)CH(CO₂C₂H₅)₂	65	NaOC₂H₅	Ethanol	11
		O——CO				
a-$C_6H_5CH_2C_6H_4$		$C_6H_5COCH₂C(C₃H₆-o)CH(CO₂C₂H₅)₂$	—	Na	Ether	653
	CH_3—C_2H_5I	$CH_3CH(C₃H₆-o)C(C₃H₆-o)(CO₂C₂H₅)₂$	—	NaOC₂H₅	Toluene	125
	C_2H_5—C_2H_5I	$C_2H_5CH(C₃H₆-o)C(CO₂C₂H₅)₂$	—	NaOC₂H₅	Toluene	125
	CH_2=CHCH₂C₆H₅I	CH_2=CHCH₂C(C₃H₆-o)CH(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
2-CH₂-methyltetrahydropyran		$CH(CH_2)_2C_2H_{7-n}$				
2-CH₂-tetrahydropyran		$C_2H_5CH_2C(CH(CH(C₃H₅)CH_{2-n})CH(CO₂C₂H₅)_2$	—	Na	None	897
		Diethyl 2-tetrahydropyran-(1-methylbutyl)malonate	—	NaH	Toluene	683
C₆, C₁₃						
$C_{12}H_{25}CH_2$	CH_3—CHCH₂Br	CH_2=CHCH₂C(CO₂C₂H₅)₂	70-85	NaOC₂H₅	Ethanol	515
		$CH_2CH(CH_3)C_2H_5$				
		$C_{13}H_{25}n$				
n-C₆H₁₃N:		$C_2H_5CH(CH_3)CH_2C(C_{12}H_{25-n})(CO_2C_2H_5)_2$	—	NaOC₂H₅	Ethanol	888
n-C₆H₁₃N:		$C_2H_5CH(CH_3)CH_2C(CO_2C_2H_5)_2$	—	NaOC₂H₅	Ethanol	888
C₇–C₉						
C_5H_9X:	$(CH_3)_2C$=CHCH₂Br	$(CH_3)_2C$=CHCH₂C(C₃H₅)(CO₂C₂H₅)₂	65	NaOC₂H₅	$(C_2H_5O)_2CO$	663
n-C₅H₉X:	$(CH_3)_2C$=CHCH₂Br	$(CH_3)_2C$=CHCH₂C(C₃H₅-n)(CO₂C₂H₅)₂	80	NaOC₂H₅	$(C_2H_5O)_2CO$	663
s-C₅H₉Br:	$(CH_3)_2C$=CHCH₂Br	$(CH_3)_2C$=CHCH₂C(C₃H₅-s)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	912

Substrate	Halide/Reagent	Product	Yield %	Base	Solvent	Reference
	CH₂=CHCH₂Br	(CH₃)₂C=CHCH₂C(CO₂C₂H₅)₂ | CH₂CH=CH₂	71	NaOC₂H₅	Ethanol	912
	n-C₄H₉X‡	(CH₃)₂C=CHCH₂C(C₄H₉-n)(CO₂C₂H₅)₂	85	NaOC₂H₅	(C₂H₅O)₂CO	663
	sec-C₄H₉X‡	(CH₃)₂C=CHCH₂C(C₄H₉-sec)(CO₂C₂H₅)₂	65	NaOC₂H₅	(C₂H₅O)₂CO	663
	(CH₃)₂C=CHCH₂Br	[(CH₃)₂C=CHCH₂]₂C(CO₂C₂H₅)₂	80	NaOC₂H₅	(C₂H₅O)₂CO	663
	Not stated	(CH₃)₂C=CHCH₂C(C₅H₁₁-cyclo)(CO₂C₂H₅)₂	65	NaOC₂H₅	(C₂H₅O)₂CO	663
	C₆H₅CH₂X‡	(CH₃)₂C=CHCH₂C(CH₂C₆H₅)(CO₂C₂H₅)₂	85	NaOC₂H₅	(C₂H₅O)₂CO	663
(CH₂)₂CO₂C₂H₅	Br(CH₂)₂CO₂C₂H₅	(C₂H₅O₂CCH₂CH₂)₂C(CO₂C₂H₅)₂	14	NaOC₂H₅	Ethanol	670
	BrCH₂CHCH₂CO₂C₂H₅	C₂H₅O₂CCH₄CH(CO₂C₂H₅)CH₂C-(CO₂C₂H₅)₂(CH₂)₂CO₂C₂H₅	55	NaOC₂H₅	Ethanol	671
CH(CH₃)CO₂C₂H₅	CH₃I	C₂H₅O₂CCH(CH₃)C(CH₃)(CO₂C₂H₅)₂	—	Na	None	101
	C₂H₅I	C₂H₅O₂CCH(CH₃)C(C₂H₅)(CO₂C₂H₅)₂	—	Na	None	102
	C₆H₅CH₂Cl	C₂H₅O₂CCH(CH₃)C(CH₂C₆H₅)(CO₂C₂H₅)₂	—	Na	None	923

C₂–C₁₁

Substrate	Halide/Reagent	Product	Yield %	Base	Solvent	Reference
Cyclopentyl(=C₅H₉)	C₂H₅Br	C₅H₉C(C₂H₅)(CO₂C₂H₅)₂	48	NaOC₂H₅	Ethanol	148
	n-C₇H₁₅Br	n-C₇H₁₅C(C₅H₉)(CO₂C₂H₅)₂	50–60	Na	C₆H₆	725
	n-C₈H₁₇Br	n-C₈H₁₇C(C₅H₉)(CO₂C₂H₅)₂	50–60	Na	C₆H₆	725
	n-C₉H₁₉Br	n-C₉H₁₉C(C₅H₉)(CO₂C₂H₅)₂	50–60	Na	C₆H₆	725
	n-C₁₀H₂₁Br	n-C₁₀H₂₁C(C₅H₉)(CO₂C₂H₅)₂	50–60	Na	C₆H₆	725
	Geranyl bromide	Diethyl cyclopentyl(geranyl)malonate	25	NaOC₂H₅	Ethanol	31
	n-C₁₁H₂₃Br	n-C₁₁H₂₃C(C₅H₉)(CO₂C₂H₅)₂	50–60	Na	C₆H₆	725

C₂–C₅

Substrate	Halide/Reagent	Product	Yield %	Base	Solvent	Reference
2-Cyclopentenyl (=C₅H₇)	C₂H₅Br	C₅H₇C(C₂H₅)(CO₂H)₂	30	Na	Toluene	151
	n-C₃H₇Br	C₅H₇C(C₃H₇-n)(CO₂H)₂	26	Na	Toluene	151
	i-C₃H₇Br	C₅H₇C(C₃H₇-i)(CO₂H)₂	8	Na	Toluene	151
	CH₂=CHCH₂Br	CH₂=CHCH₂C(C₅H₇)(CO₂H)₂	32	Na	Toluene	151
	n-C₄H₉Br	n-C₄H₉C(C₅H₇)(CO₂H)₂	35	Na	Toluene	151
	n-C₅H₁₁Br	n-C₅H₁₁C(C₅H₇)(CO₂C₂H₅)₂	37	NaOC₂H₅	Ethanol	630
	2-Cyclopentenyl chloride	(C₅H₇)₂C(CO₂C₂H₅)₂	50	Na	Toluene	151, 925, 926

Note: References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
n-C₅H₁₁ (Cont.)	**C₅–C₆**					
	CH₃CHBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)C(C₅H₁₁-*n*)(CO₂C₂H₅)₂	24	NaOC₂H₅	Ethanol	223
	2-Chloromethylthiophene	C₂H₅SCH₂C(C₅H₁₁-*n*)(CO₂C₂H₅)₂	0	Na	None	807
	C₂H₅CHBrCO₂C₂H₅	C₂H₅O₂CCH(C₂H₅)C(C₅H₁₁-*n*)(CO₂C₂H₅)₂	11	NaOC₂H₅	Ethanol	223
	(CH₃)₂CHBrCO₂C₂H₅	C₂H₅O₂CC(CH₃)₂C(C₅H₁₁-*n*)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	223
	i-C₃H₅CHBrCO₂C₂H₅	C₂H₅CHCH—CH₂ (epoxide) C(C₅H₁₁-*n*)CO₂C₂H₅	65	NaOC₂H₅	Ethanol	11
n-C₅H₁₁CH(CH₃)	C₆H₅COCH₂Br	C₂H₅COCH₂C[(C₅H₁₁-*i*)](CO₂C₂H₅)₂	—	Na	Ether	653
	CH₃SCH₂Cl	CH₃SCH₂C[CH(CH₃)C₅H₁₁-*n*](CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	C₂H₅SCH₂Cl	C₂H₅SCH₂C[CH(CH₃)C₅H₁₁-*n*](CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
	CH₂=CHCH₂SCH₂Cl	CH₂=CHCH₂SCH₂C(CO₂C₂H₅)₂ CH(CH₃)C₅H₁₁-*n*	—	NaOC₂H₅	Toluene	125
	2-Chloromethylthiophene	C₂H₅SCH₂C[CH(CH₃)C₅H₁₁-*n*](CO₂C₂H₅)₂	—	Na	None	807
	2-Chlorotetrahydropyran	Diethyl 2-tetrahydropyranyl-(1-methylbutyl)malonate	—	NaH	Toluene	083
C₂H₅CH(CH₃)CH₂	**C₃–C₁₂**					
	CH₂=CHCH₂Br	CH₂=CHCH₂C(CO₂C₂H₅)₂ CH₂CH(CH₃)C₂H₅	70–85	NaOC₂H₅	Ethanol	545
	n-C₁₀H₂₁X‡	C₂H₅CH(CH₃)CH₂C(C₁₀H₂₁-*n*)(CO₂C₂H₅)₂ C₁₂H₂₅-*n*	—	NaOC₂H₅	Ethanol	888
	n-C₁₃H₂₅X‡	C₂H₅CH(CH₃)CH₂C(C(C₁₀H₂₁-*n*)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	888
(CH₃)₂C=CHCH₂	**C₃–C₇**					
	C₂H₅X‡	(CH₃)₂C=CHCH₂C(C₂H₅)(CO₂C₂H₅)₂	05	NaOC₂H₅	(C₂H₅O)₂CO	003
	n-C₃H₇X‡	(CH₃)₂C=CHCH₂C(C₃H₇-*n*)(CO₂C₂H₅)₂	80	NaOC₂H₅	(C₂H₅O)₂CO	003
	i-C₃H₇Br	(CH₃)₂C=CHCH₂C(C₃H₇-*i*)(CO₂C₂H₅)₂	Poor	NaOC₂H₅	Ethanol	912

Halide (group)	Halide	Product	%	Base	Solvent	Reference
$CH_2=CHCH_2Br$		$(CH_3)_2C=CHCH_2C(CO_2C_2H_5)_2$ (with $CH_2CH=CH_2$)			Ethanol	912
	$n\text{-}C_3H_6X\ddagger$	$(CH_3)_2C=CHCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	85	$NaOC_2H_5$	$(C_2H_5O)_2CO$	663
	$sec\text{-}C_4H_9X\ddagger$	$(CH_3)_2C=CHCH_2C(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	65	$NaOC_2H_5$	$(C_2H_5O)_2CO$	663
	$(CH_3)_2C=CHCH_2Br$	$[(CH_3)_2C=CHCH_2]_2C(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	$(C_2H_5O)_2CO$	663
	Not stated	$(CH_3)_2C=CHCH_2C(C_4H_{11}\text{-}cyclo)(CO_2C_2H_5)_2$	65	$NaOC_2H_5$	$(C_2H_5O)_2CO$	663
	$C_6H_5CH_2X\ddagger$	$(CH_3)_2C=CHCH_2C(CCH_2C_6H_5)(CO_2C_2H_5)_2$	85	$NaOC_2H_5$	$(C_2H_5O)_2CO$	663
$(CH_2)_2CO_2C_2H_5$	$Br(CH_2)_2CO_2C_2H_5$	$(C_2H_5O_2CCH_2CH_2)_2C(CO_2C_2H_5)_2$	11	$NaOC_2H_5$	Ethanol	670
	$BrCH_2CHCH_2CO_2C_2H_5$ (with $CO_2C_2H_5$)	$C_2H_5O_2CCH_2CH(CO_2C_2H_5)CH_2C\text{-}(CO_2C_2H_5)_2(CH_2)_2CO_2C_2H_5$	55	$NaOC_2H_5$	Ethanol	671
$CH(CH_3)CO_2C_2H_5$	CH_3I	$C_2H_5O_2CCH(CH_3)C(CH_3)(CO_2C_2H_5)_2$	—	Na	None	161
	C_2H_5I	$C_2H_5O_2CCH(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	None	162
	$C_6H_5CH_2Cl$	$C_2H_5O_2CCH(CH_3)C(CH_2C_6H_5)(CO_2C_2H_5)_2$	—	Na	None	923
Cyclopentyl($=C_5H_9$)	C_2H_5Br (C_2–C_{11})	$C_2H_5C(C_5H_9)(CO_2C_2H_5)_2$	48	$NaOC_2H_5$	Ethanol	148
	$n\text{-}C_3H_7Br$	$n\text{-}C_3H_7C(C_5H_9)(CO_2C_2H_5)_2$	50–60	Na	C_6H_6	725
	$n\text{-}C_8H_{17}Br$	$n\text{-}C_8H_{17}C(C_5H_9)(CO_2C_2H_5)_2$	50–60	Na	C_6H_6	725
	$n\text{-}C_9H_{19}Br$	$n\text{-}C_9H_{19}C(C_5H_9)(CO_2C_2H_5)_2$	50–60	Na	C_6H_6	725
	$n\text{-}C_{10}H_{21}Br$	$n\text{-}C_{10}H_{21}C(C_5H_9)(CO_2C_2H_5)_2$	50–60	Na	C_6H_6	725
	Geranyl bromide	Diethyl cyclopentyl(geranyl)malonate	25	$NaOC_2H_5$	Ethanol	31
	$n\text{-}C_{11}H_{23}Br$	$n\text{-}C_{11}H_{23}C(C_5H_9)(CO_2C_2H_5)_2$	50–60	Na	C_6H_6	725
2-Cyclopentenyl ($=C_5H_7$)	C_2H_5Br (C_2–C_5)	$C_5H_7C(C_2H_5)(CO_2H)_2$	30	Na	Toluene	151
	$n\text{-}C_3H_7Br$	$C_3H_7C(C_3H_7\text{-}n)(CO_2H)_2$	20	Na	Toluene	151
	$i\text{-}C_3H_7Br$	$C_5H_7C(C_3H_7\text{-}i)(CO_2H)_2$	8	Na	Toluene	151
	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_3H_7)(CO_2H)_2$	32	Na	Toluene	151
	$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(C_5H_7)(CO_2H)_2$	35	Na	Toluene	151
	$n\text{-}C_5H_{11}Br$	$n\text{-}C_5H_{11}C(C_5H_7)(CO_2C_2H_5)_2$	37	$NaOC_2H_5$	Ethanol	630
	2-Cyclopentenyl chloride	$(C_5H_7)_2C(CO_2C_2H_5)_2$	50	Na	Toluene	151, 925, 920

Note: References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
2-Cyclopentenyl (~C₅H₇) (*Cont.*)						
C₃–C₄						
	n-C₃H₁₅Br	n-C₅H₁₅C((C₃H₇)(CO₂C₂H₅)₂	39	NaOC₂H₅	Ethanol	080
	Br(CH₂)₆Br	Br(CH₂)₆(C₅H₇)(CO₂C₂H₅)₂	10	Na	Xylene	079
		(C₅H₇O₂C(CH₂)₆C(CO₂C₂H₅)₂	22			
	1,2-Dibromocyclohexane	Diethyl 2-cyclohexenyl-1-(2-cyclopentenyl)- malonate	53	NaOC₂H₅	Toluene	927
	n-C₇H₁₅Br	n-C₇H₁₅C(C₅H₇)(CO₂C₂H₅)₂	35	NaOC₂H₅	Ethanol	080
	C₆H₅CH₂Cl	C₆H₅CH₂C(C₅H₇)(CO₂C₂H₅)₂	67	Na	Toluene	927
	n-C₅H₁₇Br	n-C₅H₁₇C(C₅H₇)(CO₂C₂H₅)₂	34	NaOC₂H₅	Ethanol	080
	n-C₄H₉CH(C₂H₅)CH₂Br	n-C₄H₉CH(C₂H₅)CH₂C(C₅H₇)(CO₂C₂H₅)₂	50	Na	Xylene	914
C₉–C₁₈						
	n-C₉H₁₉Br	n-C₉H₁₉C(C₅H₇)(CO₂C₂H₅)₂	42	NaOC₂H₅	Ethanol	080
	n-C₁₀H₂₁Br	n-C₁₀H₂₁C(C₅H₇)(CO₂C₂H₅)₂	00–00	NaOC₂H₅	Ethanol	928
	Geranyl chloride	Diethyl geranyl-(2-cyclopentenyl)malonate	30	NaOC₂H₅	Ethanol	31
	n-C₁₁H₂₃Br	n-C₁₁H₂₃C(C₅H₇)(CO₂C₂H₅)₂	00–00	NaOC₂H₅	Ethanol	928
	n-C₁₂H₂₅Br	n-C₁₂H₂₅C(C₅H₇)(CO₂C₂H₅)₂	00–00	NaOC₂H₅	Ethanol	928
	n-C₁₆H₃₃Br	n-C₁₆H₃₃C(C₅H₇)(CO₂C₂H₅)₂	64	Na	Xylene	079
	Hydnocarpyl bromide-KI	Diethyl hydnocarpyl-(2-cyclopentenyl)- malonate	30	K	Toluene	287
(image: 3-methyltetrahydrofuran)	CH₃Br	(image) (CH₂)₂C((CO₂C₂H₅)₂	36	NaOC₂H₅	Ethanol	082
(image: methyltetrahydrofuran)	ClCH₂CO₂C₂H₅	(image) CH₂C(CO₂C₂H₅)₂ CH₂CO₂C₂H₅	40	NaOC₂H₅	Ethanol	356

Reactant	Product	% Yield	Base	Solvent	Reference
$\begin{array}{c}\text{CH}_3\\ \boxed{}_S\end{array}$ (···C_3H_5S)					
C_2–C_6					
C_2H_5Br	$C_3H_5SC(C_2H_5)(CO_2C_2H_5)_2$	72	$NaOC_2H_5$	Ethanol	358
2-Cyclopentenyl chloride	Diethyl 2-cyclopentenyl-(2-thenyl)-malonate	54	$NaOC_2H_5$	Ethanol	924
2-Chloromethylthiophene	$(C_2H_5S)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	50
2-Cyclohexenyl bromide	Diethyl 2-cyclohexenyl-(2-theny)malonate	70	$NaOC_2H_5$	Ethanol	924
β-2-(Thienyl)ethyl chloride	Diethyl[β-(2-thienyl)ethyl]-2-thenyl-malonate	—	$NaOC_2H_5$	Ethanol	50
$C_2H_5CH_2Cl$	$C_2H_5CH_2C(C_2H_5S)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	50
β-Cyclohexylethyl bromide	Diethyl (β-cyclohexylethyl)-2-thenyl-malonate	—	$NaOC_2H_5$	Ethanol	50
C_3–C_6					
$CH_2{-}CH_2$ (epoxide, O)	$(CH_2)_2C(C_6H_{11}a\text{-}n)CO_2C_2H_5$ (O—CO)	ca.70	$NaOC_2H_5$	Ethanol	282
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_6H_{13}a\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_6H_{13}\text{-}n)(CO_2C_2H_5)_2$	—	—	—	743
$C_2H_5SCH(CH_3)Cl$	$C_2H_5SCH(CH_3)C(C_6H_{13}a\text{-}n)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	126
2-Chloromethylthiophene	$C_7H_5SCH_2C(C_6H_{13}a\text{-}n)(CO_2C_2H_5)_2$	—	Na	None	897
$n\text{-}C_6H_{13}Br$	$(C_6H_{13}\text{-}n)_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	941
C_7–C_9					
$n\text{-}C_7H_{15}X\ddagger$	$n\text{-}C_7H_{15}C(C_6H_{13}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
β-Cyclopentenylethyl bromide	Diethyl n-hexyl-(β-cyclopentylethyl)-	50–60	$NaOC_2H_5$	Ethanol	725
β-(2-Cyclopentenyl)ethyl bromide	Diethyl n-hexyl-[β-(2-cyclopentenyl)ethyl]-malonate	—	$NaOC_2H_5$	Ethanol	928
$n\text{-}C_6H_{17}Br$	$n\text{-}C_6H_{17}C(C_6H_{13}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	888
β-Cyclohexylethyl bromide	Diethyl n-hexyl-(β-cyclohexylethyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
$n\text{-}C_9H_{11}X\ddagger$	$n\text{-}C_9H_{19}C(C_6H_{11}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	887
γ-Cyclohexylpropyl bromide	Diethyl n-hexyl-(γ-cyclohexylpropyl)-malonate	—	$NaOC_2H_5$	Ethanol	902

Note: References 577–1090 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
2-Cyclopentenyl $(=C_5H_7)$ (Cont.)	C_6–C_8					
	n-$C_6H_{13}Br$	n-$C_6H_{13}C(C_5H_7)(CO_2C_2H_5)_2$	39	$NaOC_2H_5$	Ethanol	680
	$Br(CH_2)_6Br$	$(Br(CH_2)_6C(C_5H_7)(CO_2C_2H_5)_2$	10	Na	Xylene	679
		$((C_2H_5O_2C)_2C(CH_2)_6C(CO_2C_2H_5)_2$	22			
	1,2-Dibromocyclohexane	Diethyl 2-cyclohexenyl-(2-cyclopentenyl)-malonate $\overset{C_5H_7\quad C_5H_7}{\vert\qquad\vert}$	53	$NaOC_2H_5$	Toluene	927
	n-$C_7H_{15}Br$	n-$C_7H_{15}C(C_5H_7)(CO_2C_2H_5)_2$	35	$NaOC_2H_5$	Ethanol	680
	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_5H_7)(CO_2C_2H_5)_2$	67	Na	Toluene	927
	n-$C_8H_{17}Br$	n-$C_8H_{17}C(C_5H_7)(CO_2C_2H_5)_2$	34	$NaOC_2H_5$	Ethanol	680
	n-$C_4H_9CH(C_2H_5)CH_2Br$	n-$C_4H_9CH(C_2H_5)CH_2C(C_5H_7)(CO_2C_2H_5)_2$	56	Na	Xylene	914
	C_9–C_{16}					
	n-$C_9H_{19}Br$	n-$C_9H_{19}C(C_5H_7)(CO_2C_2H_5)_2$	42	$NaOC_2H_5$	Ethanol	680
	n-$C_{10}H_{21}Br$	n-$C_{10}H_{21}C(C_5H_7)(CO_2C_2H_5)_2$	66–69	$NaOC_2H_5$	Ethanol	928
	Geranyl chloride	Diethyl geranyl-(2-cyclopentenyl)malonate	30	$NaOC_2H_5$	Ethanol	31
	n-$C_{11}H_{23}Br$	n-$C_{11}H_{23}C(C_5H_7)(CO_2C_2H_5)_2$	66–69	$NaOC_2H_5$	Ethanol	928
	n-$C_{12}H_{25}Br$	n-$C_{12}H_{25}C(C_5H_7)(CO_2C_2H_5)_2$	66–69	$NaOC_2H_5$	Ethanol	928
	n-$C_{16}H_{33}Br$	n-$C_{16}H_{33}C(C_5H_7)(CO_2C_2H_5)_2$	64	Na	Xylene	679
	Hydnocarpyl bromide-KI	Diethyl hydnocarpyl-(2-cyclopentenyl)-malonate	38	K	Toluene	287
(cyclopentyl-CH₂)	(cyclopentyl-CH₂)Br	$\Big(\overset{cyclopentyl}{CH_2}\Big)_2C(CO_2C_2H_5)_2$	36	$NaOC_2H_5$	Ethanol	682
(cyclopentyl-CH₂)	$ClCH_2CO_2C_2H_5$	$(cyclopentyl)CH_2C(CO_2C_2H_5)_2$ $CH_2CO_2C_2H_5$	40	$NaOC_2H_5$	Ethanol	356

Halide	Product	Yield (%)	Metalating agent	Solvent	References
i-C_3H_7Br	$(C_2H_5)_2CHCH_2C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	—	—	—	687
CH_2=$CHCH_2$Br	$(C_2H_5)_2CHCH_2C(CH_2CH$=$CH_2)(CO_2C_2H_5)_2$	—	—	—	687
HC≡CCH_2Br	$(C_2H_5)_2CHCH_2C(CH_2C$≡$CH)(CO_2C_2H_5)_2$	—	—	—	687
CH_2=$CBrCH_2$Br	$(C_2H_5)_2CHCH_2C(CH_2CBr$=$CH_2)(CO_2C_2H_5)_2$	—	—	—	687
C_4–C_6					
n-C_4H_9Br	$(C_2H_5)_2CHCH_2C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	—	—	—	687
i-C_4H_9Br	$(C_2H_5)_2CHCH_2C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	—	—	—	687
$(C_4H_9)_2CHCH_2$Br	$[(C_4H_9)_2CHCH_2]_2C(CO_2C_2H_5)_2$	—	—	—	687
1,2-Dibromocyclohexane	Diethyl 2-cyclohexenyl-(2-ethylbutyl)-malonate	—	—	—	687
cis-C_2H_5CH=CHCH(CH$_3$)					
CH_2=$CHCH_2$Br	cis-C_2H_5CH=CHCH(CH$_3$)-$C(CH_2CH$=$CH_2)(CO_2C_2H_5)_2$	77	Na	—	693
$C_2H_5O_2CCH(C_2H_5)$					
CH_3I	$C_2H_5O_2CCH(C_2H_5)C(CH_3)(CO_2C_2H_5)_2$	—	Na	None	162
C_2H_5I	$C_2H_5O_2CCH(C_2H_5)C(C_2H_5)(CO_2C_2H_5)_2$	—	Na	None	162
$C_6H_5CH_2$Cl	$C_2H_5O_2CCH(C_2H_5)C(CH_2C_6H_5)(CO_2C_2H_5)_2$	—	Na	None	162
$C_2H_5O_2CC(CH_3)_2$ **C_1–C_7**					
CH_3I	$C_2H_5O_2CC(CH_3)_2C(CH_3)(CO_2C_2H_5)_2$	—	Na	None	162
$C_6H_5CH_2$Cl	$C_2H_5O_2CC(CH_3)_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	—	Na	None	162
[thiophene]–CH_2Cl	$C_4H_3S(CH_2)_2C(CH_2SC_4H_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	50, 708
Cyclohexyl(=C_6H_{11}) **C_2–C_6**					
C_2H_5X‡	$C_6H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	58	$NaOC_4H_9\text{-}t$	t-C_4H_9OH	35
CH_2=$CHCH_2$Br	CH_2=$CHCH_2C(C_6H_{11})(CO_2C_2H_5)_2$	—	—	—	743
n-C_4H_9Br	n-$C_4H_9C(C_6H_{11})(CO_2C_2H_5)_2$	Poor	—	—	926
n-C_5H_{11}Br	n-$C_5H_{11}C(C_6H_{11})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	—
2-Chloromethylthiophene	$C_4H_3SCH_2C(C_6H_{11})(CO_2C_2H_5)_2$	68	$NaOC_2H_5$	$(C_2H_5O)_2CO$	50, 709
n-C_6H_{13}Br	n-$C_6H_{13}C(C_6H_{11})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
Cyclohexyl bromide	$(C_6H_{11})_2C(CO_2C_2H_5)_2$	—	Na	Toluene	147
Cyclohexyl bromide	None	—	$NaOC_2H_5$	Ethanol	149
C_7–C_{12}					
n-C_7H_{15}Br	n-$C_7H_{15}C(C_6H_{11})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
$(CH_3)_3CC(CH_3)_2$Cl	$(C_2H_5O_2C)_2C(C_6H_{11})(CO_2C_2H_5)_2$	15	$NaOC_2H_5$	Ethanol	719
n-C_8H_{17}Br	n-$C_8H_{17}C(C_6H_{11})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32

Note: References 577–1080 are on pp. 322–331.

‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_{10}–C_{18}						
n-C_6H_{13} (*Cont.*)	n-$C_{10}H_{21}I$	n-$C_{10}H_{21}C(C_6H_{13}$-$n)(CO_2C_2H_5)_2$	70	Na	Toluene	906, 888
	δ-Cyclohexylbutyl bromide	Diethyl n-hexyl-(δ-cyclohexylbutyl)-malonate	—	$NaOC_2H_5$	Ethanol	902
	n-Undecenyl bromide	Diethyl n-hexyl-(n-undecenyl)malonate	—	$NaOC_2H_5$	Ethanol	920
	n-$C_{16}H_{33}I$	n-$C_{16}H_{33}C(C_6H_{13}$-$n)(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	Ethanol	135
	n-$C_{18}H_{37}I$	n-$C_{18}H_{37}C(C_6H_{13}$-$n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	684
$CH_3CHBr(CH_2)_4$	None	Diethyl 2-methylcyclohexane-1,1-dicarboxylate	45	$NaOC_2H_5$	Ethanol	210
$C_2H_5O(CH_2)_4$	$C_2H_5O(CH_2)_4Br$	$[C_2H_5O(CH_2)_4]_2C(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Ethanol	646
n-$C_3H_7CH(CH_3)$	CH_2=$CHCH_2Br$	n-$C_3H_7CH(CH_3)C(CH_2CH$=$CH_2)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	551
$Br(CH_2)_4CH(CH_3)$	None	Diethyl 2-methyleylcyclohexane-1,1-dicarboxylate	72	$NaOC_2H_5$	Ethanol	210
3-Hexyl	$CH_3X\ddagger$	Diethyl methyl-(3-hexyl)malonate	62	$NaOC_4H_9$-t	t-C_4H_9OH	35
	$C_2H_5X\ddagger$	Diethyl ethyl-(3-hexyl)malonate	76	$NaOC_4H_9$-t	t-C_4H_9OH	35
n-$C_3H_7CH(CH_3)CH_2$	$Br(CH_2)_2Br$	$CH_2CH_2C[CH_2CH(CH_3)C_3H_7$-$n]CO_2C_2H_5$ O——CO	85	Na	C_6H_6	555
i-$C_4H_9CH(CH_3)$	2-Chloromethylthiophene	i-$C_4H_9CH(CH_3)C(CH_2C_4H_3S)(CO_2C_2H_5)_2$	—	Na	None	897
C_1–C_3						
$(C_2H_5)_2CHCH_2$	CH_3Br	$(C_2H_5)_2CHCH_2C(CH_3)(CO_2C_2H_5)_2$	—	—	—	687
	C_2H_5Br	$(C_2H_5)_2CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	77	$NaOC_2H_5$	Ethanol	088, 687
	$Br(CH_2)_2Br$	$CH_2CH_2C[CH(CH_2CH(C_2H_5)_2]CO_2C_2H_5$ O——CO	91	Na	C_6H_6	555
	CH_2—CH_2 (epoxide, O)	$CH_2CH_2C[CH(C_2H_5)_2]CO_2C_2H_5$ O——CO	ca. 70	$NaOC_2H_5$	Ethanol	282
	n-C_3H_7X	$(C_2H_5)_2CHCH_2C(C_3H_7$-$n)(CO_2C_2H_5)_2$	—	—	—	687

Alkyl halide	Product	%	Base	Solvent	Ref.
C_3					
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_6H_5)(CO_2C_2H_5)_2$	48	Na	Ether	205
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_6H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$CH_2{=}CHCH_2I$	$CH_2{=}CHCH_2C(C_6H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	70
$Cl(CH_2)_2CN$	$NC(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	32	$NaOC_2H_5$	Ethanol	932
$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_6H_5)(CO_2C_2H_5)_2$	—	Na	None	120
$I(CH_2)_3I$	None	—	$NaOC_2H_5$	Ethanol	92
C_4					
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(C_6H_5)(CO_2C_2H_5)_2$	58	$NaOC_2H_5$	Ethanol	142
$CH_2{=}CHO(CH_2)_2Cl$	$CH_2{=}CHO(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	62	Na	Ether	331
$C_2H_5S(CH_2)_2Cl$	$C_2H_5S(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	70-00	$NaOC_2H_5$	Toluene	553
$I(CH_2)_3CN$	$NC(CH_2)_3C(C_6H_5)(CO_2C_2H_5)_2$	>43	Na	Toluene	92
$C_5\text{-}C_8$					
2-Chloromethylthiophene	Diethyl phenyl-(2-thenyl)malonate	—	$NaOC_2H_5$	Ethanol	50
2-Chlorotetrahydropyran	Diethyl phenyl-(2-tetrahydropyranyl) malonate	—	NaH	Toluene	083
$Br(CH_2)_6Br$	$(C_2H_5O_2C)_2\underset{C_6H_5}{C}(CH_2)_6\underset{C_6H_5}{C}(CO_2C_2H_5)_2$	—	Na	Xylene	070
2 Cyclohexenyl bromide	Diethyl phenyl-(2-cyclohexenyl)malonate	55	$KOCH_3$	C_6H_6	534
1,2 Dibromocyclohexane	Diethyl phenyl-(2-cyclohexenyl)malonate	55	$NaOC_2H_5$	Ethanol	911, 933
$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_6H_5)(CO_2C_2H_5)_2$	55	$NaOC_2H_5$	Ethanol	182
$C_6H_5CH(CH_3)I$	$C_6H_5CH(CH_3)C(C_6H_5)(CO_2C_2H_5)_2$	—	—	—	034
$C_6H_5O(CH_2)_2Cl$	$C_6H_5O(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	—	—	—	374
$C_9\text{-}C_{10}$					
$C_6H_5CH(C_2H_5)I$	$C_6H_5CH(C_2H_5)C(C_6H_5)(CO_2C_2H_5)_2$	—	—	—	934
$I(CH_2)_2CH(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2CH(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	91	Na	Toluene	92
$p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2Br$	$p\text{-}t\text{-}C_4H_9C_6H_4(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	46	Na	Toluene	321
$I(CH_2)_{10}CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_{10}C(C_6H_5)(CO_2C_2H_5)_2$	—	Na	Toluene	92
β-(p-Cyclohexylphenyl)ethyl bromide	Diethyl phenyl-[β-(p-cyclohexylphenyl) ethyl]malonate	44	Na	Xylene	935
$n\text{-}C_{16}H_{33}Br$	$n\text{-}C_{16}H_{33}C(C_6H_5)(CO_2C_2H_5)_2$	42	Na	Xylene	070

Note: References 577–1080 are on pp. 322–331.
* The dimethyl ester was used in this experiment.
‖‖ The reactants were added in inverse order.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
Cyclohexyl(=C₆H₁₁) (Cont.)	β-Cyclohexylethyl bromide	Diethyl cyclohexyl-(β-cyclohexylethyl)malonate	—	NaOC₂H₅	Ethanol	929
	n-C₆H₁₃Br	n-C₆H₁₃C(C₆H₁₁)(CO₂C₂H₅)₂	45	Na	Xylene	31
	n-C₆H₁₃Br	n-C₆H₁₃C(C₆H₁₁)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	32
	n-C₁₀H₂₁Br	n-C₁₀H₂₁C(C₆H₁₁)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	32
	Geranyl chloride	Diethyl cyclohexyl-(geranyl)malonate	—	Na	Toluene	930
	n-C₁₁H₂₃Br	n-C₁₁H₂₃C(C₆H₁₁)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	32
	n-C₁₂H₂₅Br	n-C₁₂H₂₅C(C₆H₁₁)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	32
	C₂H₅SCH₂Cl	C₂H₅SCH₂C(C₆H₉)(CO₂C₂H₅)₂	—	NaOC₂H₅	Toluene	125
1-Cyclohexenyl (=C₆H₉)	CH₂=CHCH₂Br	CH₂=CHCH₂C(C₆H₉)(CO₂C₂H₅)₂	40	NaOC₂H₅	Ethanol	215
	2-Chloromethylthiophene	C₄H₃SCH₂C(C₆H₉)(CO₂C₂H₅)₂	—	Na	None	897
	Hydnocarpyl bromide-KI	Diethyl hydnocarpyl-(2-cyclohexenyl)malonate	58	K	Toluene	287
2-Cyclohexenyl						
Phenyl C₁	CH₃I	C₆H₅C(CH₃)(CO₂C₂H₅)₂	90‖	NaOC₂H₅	Ethanol	169
	CH₃I	C₆H₅C(CH₃)(CO₂C₂H₅)₂	60	NaOC₂H₅	Ethanol	182
C₂	C₂H₅Cl	C₆H₅C(C₂H₅)(CO₂C₂H₅)₂	81	NaOC₂H₅	(C₂H₅O)₂CO	51
	C₂H₅Br	C₆H₅C(C₂H₅)(CO₂C₂H₅)₂	97‖	NaOC₂H₅	Ethanol	42, 755
	C₂H₅Br	C₆H₅C(C₂H₅)(CO₂C₂H₅)₂	84	NaOC₂H₅	(C₂H₅O)₂CO	51, 44, 227
C₃	C₂H₅I	C₆H₅C(C₂H₅)(CO₂CH₃)₂*	70	NaOCH₃	CH₃OH	375
	C₂H₅I	C₆H₅C(C₂H₅)(CO₂C₂H₅)₂	61	NaOC₂H₅	Ethanol	331, 571
	C₂H₅I	C₆H₅C(C₂H₅)(CO₂C₂H₅)₂	90	Mg(OC₂H₅)₂	(C₂H₅O)₂CO	51, 44
	(C₂H₅O)₂CO	C₆H₅C(C₂H₅)(CO₂C₂H₅)₂	30	NaOC₂H₅	(C₂H₅O)₂CO	330, 800
	Br(CH₂)₃Br	Br(CH₂)₃C(C₆H₅)(CO₂C₂H₅)₂	59	NaH	Toluene	931
	Br(CH₂)₃Br	None	0	NaOC₂H₅	Ethanol	92
	I(CH₂)₂I	(C₂H₅O₂C)₂C(C₆H₅)C(C₆H₅)(CO₂C₂H₅)₂	20	NaOC₂H₅	Ethanol	92
	CH₂—CH₂ (O)	CH₂CH₂C(C₆H₅)CO₂C₂H₅ / O—CO	ca. 70	NaOC₂H₅	Ethanol	282

Halide	Product	Yield (%)	Reagent	Solvent	Reference
C_3					
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_6H_5)(CO_2C_2H_5)_2$	48	Na	Ether	205
$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(C_6H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	125
$CH_2=CHCH_2I$	$CH_2=CHCH_2C(C_6H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	79
$Cl(CH_2)_2CN$	$NC(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	32	$NaOC_2H_5$	Ethanol	932
$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_6H_5)(CO_2C_2H_5)_2$	—	Na	None	129
$I(CH_2)_3I$	None	—	$NaOC_2H_5$	Ethanol	92
C_4					
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(C_6H_5)(CO_2C_2H_5)_2$	58	$NaOC_2H_5$	Ethanol	142
$CH_2=CHO(CH_2)_2Cl$	$CH_2=CHO(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	52	Na	Ether	331
$C_2H_5S(CH_2)_2Cl$	$C_2H_5S(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	70–90	$NaOC_2H_5$	Toluene	553
$I(CH_2)_3CN$	$NC(CH_2)_3C(C_6H_5)(CO_2C_2H_5)_2$	>43	Na	Toluene	92
C_5–C_8					
2-Chloromethylthiophene	Diethyl phenyl-(2-thenyl)malonate	—	$NaOC_2H_5$	Ethanol	50
2-Chlorotetrahydropyran	Diethyl phenyl-(2-tetrahydropyranyl) malonate	—	NaH	Toluene	683
$Br(CH_2)_6Br$	$(C_2H_5O_2C)_2C(CH_2)_6C(CO_2C_2H_5)_2$ with C_6H_5	—	Na	Xylene	679
2 Cyclohexenyl bromide	Diethyl phenyl-(2-cyclohexenyl)malonate	55	$KOCH_3$	C_6H_6	534
1,2 Dibromocyclohexane	Diethyl phenyl-(2-cyclohexenyl)malonate	55	$NaOC_2H_5$	Ethanol	911, 933
$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_6H_5)(CO_2C_2H_5)_2$	55	$NaOC_2H_5$	Ethanol	182
$C_6H_5CH(CH_3)I$	$C_6H_5CH(CH_3)C(C_6H_5)(CO_2C_2H_5)_2$	—	—	—	934
$C_6H_5O(CH_2)_2Cl$	$C_6H_5O(CH_2)_2C(C_6H_5)(CO_2C_2H_5)_2$	—	—	—	374
C_9–C_{16}					
$C_6H_5CH(C_2H_5)I$	$C_6H_5CH(C_2H_5)C(C_6H_5)(CO_2C_2H_5)_2$	—	—	—	934
$I(CH_2)_3CH(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2CH(CH_2)_3C(C_6H_5)(CO_2C_2H_5)_2$	91	Na	Toluene	92
$p\text{-}t\text{-}C_4H_9C_6H_4CH(CH_3)_2Br$	$p\text{-}t\text{-}C_4H_9C_6H_4(CH_3)_2C(C_6H_5)(CO_2C_2H_5)_2$	46	Na	Toluene	321
$I(CH_2)_{10}CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_{10}C(C_6H_5)(CO_2C_2H_5)_2$	—	Na	Xylene	92
$\beta\text{-}(p\text{-Cyclohexylphenyl})ethyl$ bromide	Diethyl phenyl-[β-(p-cyclohexylphenyl) ethyl]malonate	44	Na	—	935
$n\text{-}C_{16}H_{33}Br$	$n\text{-}C_{16}H_{33}C(C_6H_5)(CO_2C_2H_5)_2$	42	Na	Xylene	679

Note: References 577–1080 are on pp. 324–381.

* The dimethyl ester was used in this experiment.

||| The reactants were added in inverse order.

	Halide	Product	Yield	Base	Solvent	Ref.
i-C₇H₁₅	n-Undecenyl bromide	Diethyl n-heptyl-(n-undecenyl)malonate	—	$NaOC_2H_5$	Ethanol	920
	n-C₁₀H₃₃I	$n\text{-}C_{16}H_{33}C(C_7H_{15}\text{-}n)(CO_2C_2H_5)_2$	83	$NaOC_2H_5$	Ethanol	135
	Hydnocarpyl chloride	Diethyl n-heptyl-(hydnocarpyl)malonate	00	K	Toluene	201
i-C₇H₁₅	CH₃I	$i\text{-}C_7H_{15}C(CH_3)(CO_2C_2H_5)_2$	72	$NaOC_2H_5$	Ethanol	718, 748
i-C₅H₁₁CH(CH₃)	CH₃I	$i\text{-}C_5H_{11}CH(CH_3)C(CH_3)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	718
n-C₄H₉CH(C₂H₅)	2-Chloromethylthiophene	$n\text{-}C_4H_9CH(C_2H_5)C(CH_2C_4H_3S)(CO_2C_2H_5)_2$	—	Na	None	897
C₂H₅O₂C(CH₂)₂CH(CH₃)	n-C₅H₁₁Br	$C_2H_5O_2C(CH_2)_2CH(CH_3)C(CO_2C_2H_5)_2$ | $C_5H_{11}\text{-}n$	20	$NaOC_2H_5$	Ethanol	720
C₂H₅O₂CCH₂C(CH₃)₂	C₆H₅O(CH₂)₂Br	$[C_6H_5O(CH_2)_2]_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	206
β-Cyclopentylidene-ethyl	Not stated	Diethyl ethyl-[β-(cyclopentylidene)ethyl]-malonate	70	$NaOC_2H_5$	$(C_2H_5O)_2CO$	663
C₃–C₈						
Cyclohexylmethyl (=C₇H₁₃)	C₂H₅Br	$C_2H_5C(C_7H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
	n-C₃H₇Br	$n\text{-}C_3H_7C(C_7H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
	n-C₄H₉Br	$n\text{-}C_4H_9C(C_7H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
	n-C₅H₁₁Br	$n\text{-}C_5H_{11}C(C_7H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
	2-Chloromethylthiophene	Diethyl (cyclohexylmethyl)-2-thenylmalonate	—	$NaOC_2H_5$	Ethanol	50, 709
	n-C₆H₁₃Br	$n\text{-}C_6H_{13}C(C_7H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
	n-C₇H₁₅Br	$n\text{-}C_7H_{15}C(C_7H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
	n-C₈H₁₇Br	$n\text{-}C_8H_{17}C(C_7H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	32
	β-Cyclohexylethyl bromide	Diethyl (cyclohexylmethyl)-(β-cyclohexylethyl)malonate	—	$NaOC_2H_5$	Ethanol	929
2-Methylcyclohexyl	2-Methylcyclohexyl bromide	Diethyl di-(2-methylcyclohexyl)malonate	10	Na	Toluene	147
	Geranyl chloride	Diethyl geranyl-(2-methylcyclohexyl)-malonate	—	Na	Toluene	147
C₂H₅O₂CC(CH₃)=C(CH₃)	CH₃I	$C_2H_5O_2CC(CH_3)=C(CH_3)C(CH_3)(CO_2C_2H_5)_2$	60	$NaOC_2H_5$	Ethanol	937
C₁						
C₆H₅CH₂	CH₃I	$C_6H_5CH_2C(CH_3)(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	C_6H_6	938
	CH₃I	$C_6H_5CH_2C(CH_3)(CO_2C_2H_5)_2$	03	$NaOC_2H_5$	Ethanol	144, 615, 930

Note: References 577–1080 are on pp. 322–331.
‡ The halogen was not specified.

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$C_6H_5CH_2$ (*Cont.*)	$CHCl_3$	$(C_2H_5O_2C)(CH_2C_6H_5)CHC[C(CO_2C_2H_5)_2]$ — $CH_2C_6H_5$	—	Na	—	231
C_2	C_2H_5Br	$C_6H_5CH_2C(C_2H_5)(CO_2C_2H_5)_3$	80	$NaOC_2H_5$	Ethanol	121, 141
	CH_3OCH_2Cl	$CH_3OCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	78	Na	Ether	411
	CH_3SCH_2Cl	$CH_3SCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	71	$NaOC_3H_7$-i	i-C_3H_7OH	910
	$BrCH=CHBr$	$BrCH=CHC(CH_2C_6H_5)(CO_2C_2H_5)_3$	7	K	Ether	205
	CH_2—CH_2 (O)	$CH_2CH_2C(CH_2C_6H_5)CO_2C_2H_5$, O——CO	ca. 70	$NaOC_2H_5$	Ethanol	911
						282
C_3	$C_2H_5SCH_2Cl$	$C_2H_5SCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	74	Na	Ether	205
	i-C_3H_7Br	i-$C_3H_7C(CH_2C_6H_5)(CO_2C_2H_5)_2$	23	$NaOC_2H_5$	Ethanol	144
	$Cl(CH_2)_3Br$	$(C_2H_5O_2C)_2C(CH_2C_6H_5)(CH_2)_3C(CO_2C_2H_5)_2$ — $CH_2C_6H_5$	—	$NaOC_2H_5$	Ethanol	530
C_4	n-C_4H_9Br	n-$C_4H_9C(CH_2C_6H_5)(CO_2C_2H_5)_2$	65	$NaOC_2H_5$	Ethanol	144
	n-C_4H_9I	n-$C_4H_9C(CH_2C_6H_5)(CO_2C_2H_5)_2$	90	$NaOC_2H_5$	Ethanol	142, 143
	$(n$-$C_4H_9O)_2CO$	n-$C_4H_9C(CH_2C_6H_5)(CO_2C_4H_9$-$n)¶$	80	KOC_4H_9-n	$(n$-$C_4H_9O)_2CO$	330, 890
	i-C_4H_9Br	i-$C_4H_9C(CH_2C_6H_5)(CO_2C_2H_5)_2$	47	$NaOC_2H_5$	Ethanol	144
	$ClCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C((CH_2C_6H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	108
	$CH_2CCl=CHCH_2Cl$	$CH_2CCl=CHCH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	90	$NaOC_2H_5$	Ethanol	916
C_5–C_7	n-$C_5H_{11}X$:	n-$C_5H_{11}C(CH_2C_6H_5)(CO_2C_2H_5)_2$	—	—	—	942
	i-$C_5H_{11}Br$	i-$C_5H_{11}C(CH_2C_6H_5)(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	144
	$Cl(CH_2)_2CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	85	Na	None	830

TABLE III—*Continued*

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C₈						
n-C₈H₁₇						
C₂—C₁₆						
	(C₂H₅O)₂CO	$n\text{-C}_8\text{H}_{17}\text{C(C}_2\text{H}_5)(\text{CO}_2\text{C}_2\text{H}_5)_2$	33 (50)§	NaOC₂H₅	(C₂H₅O)₂CO	890, 330
	CH₂—CH₂ (O)	$\text{CH}_2\text{CH}_2\text{C(C}_8\text{H}_{17}\text{-}n)\text{CO}_2\text{C}_2\text{H}_5$ (O—CO)	ca. 70	NaOC₂H₅	Ethanol	282
	CH₂=CHCH₂Br	$\text{CH}_2=\text{CHCH}_2\text{C(C}_8\text{H}_{17}\text{-}n)(\text{CO}_2\text{C}_2\text{H}_5)_2$	—	—	—	743
	Cyclobutylmethyl bromide	Diethyl *n*-octyl(cyclobutylmethyl)-malonate	—	NaOC₂H₅	Ethanol	947
	2-Chloromethylthiophene	$\text{C}_4\text{H}_3\text{SCH}_2\text{C(C}_8\text{H}_{17}\text{-}n)(\text{CO}_2\text{C}_2\text{H}_5)_2$	—	Na	None	897
	β-Cyclopentylethyl bromide	Diethyl *n*-octyl-(β-cyclopentylethyl)-malonate	50–60	NaOC₂H₅	Ethanol	725
	β-(2-Cyclopentenyl)ethyl bromide	Diethyl *n*-octyl-1-[β-(2-cyclopentenyl)-ethyl]malonate	—	NaOC₂H₅	Ethanol	928
	n-C₈H₁₇I	$(n\text{-C}_8\text{H}_{17})_2\text{C(CO}_2\text{C}_2\text{H}_5)_2$	60	Na	Toluene	906, 888
	β-Cyclohexylethyl bromide	Diethyl *n*-octyl-(β-cyclohexylethyl)-malonate	52	Na	Xylene	31, 902
	n-C₁₆H₃₃I	$n\text{-C}_{16}\text{H}_{33}\text{C(C}_8\text{H}_{17}\text{-}n)(\text{CO}_2\text{C}_2\text{H}_5)_2$	84	NaOC₂H₅	Ethanol	135
n-C₆H₁₃CH(CH₃)						
C₁—C₇						
	CH₃Br	$n\text{-C}_6\text{H}_{13}\text{CH(CH}_3)\text{C(CH}_3)(\text{CO}_2\text{C}_2\text{H}_5)_2$	96	—	—	746
	n-C₃H₇Br	$n\text{-C}_6\text{H}_{13}\text{CH(CH}_3)\text{C(C}_3\text{H}_7\text{-}n)(\text{CO}_2\text{C}_2\text{H}_5)_2$	85	—	—	746
	CH₂=CHCH₂Br	$n\text{-C}_6\text{H}_{13}\text{CH(CH}_3)\text{C(CO}_2\text{C}_2\text{H}_5)_2\ \text{CH}_2\text{CH}=\text{CH}_2$	70–85	NaOC₂H₅	Ethanol	545
	C₂H₅CH(CH₃)CH₂Br	$n\text{-C}_6\text{H}_{13}\text{CH(CH}_3)\text{C(CO}_2\text{C}_2\text{H}_5)_2\ \text{CH}_2\text{CH(CH}_3)\text{C}_2\text{H}_5$	60	—	—	746
	i-C₅H₁₁Br	$n\text{-C}_6\text{H}_{13}\text{CH(CH}_3)\text{C(C}_5\text{H}_{11}\text{-}i)(\text{CO}_2\text{C}_2\text{H}_5)_2$	60	Na	None	746
	2-Chloromethylthiophene	$n\text{-C}_6\text{H}_{13}\text{CH(CH}_3)\text{C(CH}_2\text{C}_4\text{H}_3\text{S)(CO}_2\text{C}_2\text{H}_5)_2$	—	Na	None	807
	n-C₇H₁₅Br	$n\text{-C}_6\text{H}_{13}\text{CH(CH}_3)\text{C(C}_7\text{H}_{15}\text{-}n)(\text{CO}_2\text{C}_2\text{H}_5)_2$	50	—	—	746

Parent	Alkyl halide	Product	Conv.	K (metal/base)	Solvent	Ref.
i-C₈H₁₇CH(CH₃)	C₂H₅O(CH₂)₂I	i-C₈H₁₇CH(CH₃)CH₂C(CO₂C₂H₅)₃	17	—	Xylene	720
n-C₄H₉CH(C₂H₅)CH₂	CH₂=CHCH₂Br	n-C₄H₉CH(C₂H₅)CH₂C((CH₂)₂OC₂H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	749
	2-Chloromethylthiophene	n-C₄H₉CH(C₂H₅)CH₂C(CH₂C₄H₃S)(CO₂C₂H₅)₂	—	—	None	597
β-Cyclohexylethyl	2-Chloromethylthiophene	Diethyl (β-cyclohexylethyl)-2-thenylmalonate	—	Na		50
β-Cyclohexylidenethyl	C₂H₅X‡	Diethyl dl-(β-cyclohexylidenethyl)malonate	90	NaOC₂H₅	(C₂H₅O)₂CO	923
	C₂H₅X‡	Diethyl methyl(β-cyclohexylidenethyl)-malonate	73	NaOC₂H₅	Ethanol	923
β-Cyclohexylidenethyl halide‡		Diethyl ethyl(β-cyclohexylidenethyl)-malonate	73	NaOC₂H₅	(C₂H₅O)₂CO	73
		Diethyl dl-(β-cyclohexylidenethyl)-malonate	63	NaOC₂H₅	(C₂H₅O)₂CO	63
C₂–C₃						
C₂H₅Br		C₆H₅(CH₂)₂C(C₂H₅)(CO₂C₂H₅)₂	55	Na	Toluene	411
C₂H₅Br		C₆H₅(CH₂)₂C(C₂H₅)(CO₂C₂H₅)₂	59	NaOC₂H₅	Ethanol	539,116
n-C₃H₇Br		C₆H₅(CH₂)₂C(C₃H₇-n)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	755
CH₃O(CH₂)₂Cl		CH₃O(CH₂)₂C((CH₂)₂C₆H₅)(CO₂C₂H₅)₂	—		—	374
i-C₃H₇Br		C₆H₅(CH₂)₂C(C₃H₇-i)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	755
CH₂=CHCH₂Br		C₆H₅(CH₂)₂C(CH₂CH=CH₂)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	735,508
C₄–C₅						
n-C₄H₉I		C₆H₅(CH₂)₂C(C₄H₉-n)(CO₂C₂H₅)₂	53	NaOC₂H₅	Ethanol	142
C₂H₅O(CH₂)₂Cl		C₂H₅O(CH₂)₂C((CH₂)₂C₆H₅)(CO₂C₂H₅)₂	—		—	374
sec-C₄H₉Cl		C₆H₅(CH₂)₂C(C₄H₉-sec)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	755
i-C₄H₉Br		C₆H₅(CH₂)₂C(C₄H₉-i)(CO₂C₂H₅)₂	70	NaOC₂H₅	Ethanol	755
CH₃CCl=CHCH₂Cl		CH₃CCl=CHCH₂C((CH₂)₂C₆H₅)(CO₂C₂H₅)₂	—	NaOC₂H₅	Ethanol	918
Cyclopentyl bromide		Diethyl cyclopentyl(β-phenylethyl)-malonate	66	K	Toluene	949

C₆H₅(CH₂)₂

Note: References 577–1080 are on pp. 322–331.
‡ The halogen was not specified.
§ Here and in subsequent cases the first figure represents the conversion; the figure in parentheses represents the yield.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$C_6H_5(CH_2)_2$ (Cont.)	Cyclopentyl bromide	Diethyl cyclopentyl-(β-phenylethyl)-malonate	75	$NaOC_2H_5$	Ethanol	949
	2-Cyclopentenyl chloride	Diethyl (β-phenylethyl)-2-cyclopentenyl-malonate	91	$NaOC_2H_5$	Ethanol	949
C_6–C_9						
	$n\text{-}C_4H_9O(CH_2)_2Cl$	$n\text{-}C_4H_9O(CH_2)_2C[(CH_2)_2C_6H_5](CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	374
	2-Methylcyclopentyl bromide	Diethyl (β-phenylethyl)-(2-methyl-cyclopentyl)malonate	54		Ethanol	949
	$C_2H_5CH_2Cl$	$C_2H_5(CH_2)_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	64	$NaOC_2H_5$	Ethanol	757
	$C_6H_5CH_2Br$	$C_6H_5(CH_2)_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	756
	β-Cyclohexylethyl bromide	Diethyl (β-phenylethyl)-(β-cyclohexyl-ethyl)malonate	—	$NaOC_2H_5$	Ethanol	755
	$C_6H_5(CH_2)_2Br$	$[C_6H_5(CH_2)_2]_2C(CO_2C_2H_5)_2$	62	Na	Toluene	757
	$C_6H_5O(CH_2)_2Cl$	$C_6H_5O(CH_2)_2C[(CH_2)_2C_6H_5](CO_2C_2H_5)_2$	—		—	374
	$C_6H_5O(CH_2)_3Cl$	$C_6H_5O(CH_2)_3C[(CH_2)_2C_6H_5](CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	757
$C_6H_5O(CH_2)_2$	$C_6H_5CH_2Cl$	$C_6H_5O(CH_2)_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	757
	$C_6H_5O(CH_2)_2X$‡	$[C_6H_5O(CH_2)_2]_2C(CO_2C_2H_5)_2$	92	$NaOC_2H_5$	Ethanol	421
$o\text{-}CH_3C_6H_4CH_2CH_2$	$BrCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(CO_2C_2H_5)(CH_2C_6H_4CH_3\text{-}o)(CO_2C_2H_5)_2$	70			945
$m\text{-}CH_3C_6H_4CH_2$	$C_6H_5CH_2Cl$	$m\text{-}CH_3C_6H_4CH_2CH_2C(CH_2C_6H_5)(CO_2C_2H_5)_2$	78	$NaOC_2H_5$	Toluene	507
$p\text{-}CH_3C_6H_4CH_2$	$CH_2{=}CHCH_2Br$	$p\text{-}CH_3C_6H_4CH_2CH_2C(CH_2CH{=}CH_2)(CO_2C_2H_5)_2$	—			763
2-Methoxy-5-nitrobenzyl	CH_3I	Diethyl methyl-(2-methoxy-5-nitrobenzyl)malonate	·-			763
	C_2H_5I	Diethyl ethyl-(2-methoxy-5-nitrobenzyl)malonate	100	$NaOC_2H_5$	Toluene	511
$p\text{-}CH_3OC_6H_4CH_2$	$CH_2{=}CHCH_2Br$	$p\text{-}CH_3OC_6H_4CH_2C(CO_2C_2H_5)_2$, branch $CH_2CH{=}CH_2$	—			
	$BrCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(CO_2C_2H_5)_2$, branch $CH_2C_6H_4OCH_3$	—			950

	Halide	Product	%	Agent	Solvent	Ref.
Piperonyl	C_2H_5Br	Diethyl ethyl(piperonyl)malonate	—	$NaOC_2H_5$	Ethanol	560
	$CH_2=CHCH_2Br$	Diethyl allyl(piperonyl)malonate	—	$NaOC_2H_5$	Ethanol	560
C_9						
$n\text{-}C_9H_{19}$	CH_2—CH_2 ＼O／	$CH_2CH_2C(C_9H_{19}\text{-}n)CO_2C_2H_5$ O——CO	ca. 70	$NaOC_2H_5$	Ethanol	282
$C_2\text{-}C_{16}$						
	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_9H_{19}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	920
	Cyclobutylmethyl bromide	Diethyl (cyclobutylmethyl)-n-nonylmalonate	—	$NaOC_2H_5$	Ethanol	947
	β-(2-Cyclopentenyl)ethyl bromide	Diethyl n-nonyl-[β-(2-cyclopentenyl)ethyl]-malonate	—	$NaOC_2H_5$	Ethanol	928
γ-Cyclohexylpropyl	$n\text{-}C_{16}H_{33}I$	$n\text{-}C_{16}H_{33}C(C_9H_{19}\text{-}n)(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	Ethanol	135
$C_6H_5(CH_2)_3$	γ-Cyclohexylpropyl bromide	Diethyl dl-(γ-cyclohexylpropyl)malonate	—	$NaOC_2H_5$	Ethanol	929
	$n\text{-}C_4H_9Br$	$C_6H_5(CH_2)_3C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	63	$NaOC_2H_5$	Ethanol	142
	$C_6H_5(CH_2)_2Br$	$C_6H_5(CH_2)_3C[(CH_2)_2C_6H_5](CO_2C_2H_5)_2$	45	$NaOC_2H_5$	Ethanol	709
	$C_6H_5(CH_2)_3Br$	$[C_6H_5(CH_2)_3]_2C(CO_2C_2H_5)_2$	02	Na	Toluene	708
$C_1\text{-}C_9$						
$C_6H_5O(CH_2)_3$	CH_3I	$C_6H_5O(CH_2)_3C(CH_3)(CO_2C_2H_5)_2$	73	$NaOCH_3$	CH_3OH	581
	C_2H_5I	$C_6H_5O(CH_2)_3C(C_2H_5)(CO_2C_2H_5)_2$	69	$NaOC_2H_5$	Ethanol	772
	$n\text{-}C_3H_7I$	$C_6H_5O(CH_2)_3C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	67	$NaOC_3H_7\text{-}n$	$n\text{-}C_3H_7OH$	774
	$C_6H_5O(CH_2)_3Br$	$[C_6H_5O(CH_2)_3]_2C(CO_2C_2H_5)_2$	00	$NaOC_2H_5$	Ethanol	775, 374
$C_6H_5CH_2O(CH_2)_2$	C_2H_5I	$C_6H_5CH_2O(CH_2)_2C(C_2H_5)(CO_2C_2H_5)_2$	—	—	—	374
$C_6H_5CH=CHCH_2$	C_2H_5Br	$C_6H_5CH=CHCH_2C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	755
$m\text{-}CH_3C_6H_4(CH_2)_2$	$CH_3CCl=CHCH_2Cl$	$m\text{-}CH_3C_6H_4(CH_2)_2C(CO_2C_2H_5)_2$ $CH_2CH=CClCH_3$	93	$NaOC_2H_5$	Ethanol	517
$m\text{-}CH_3OC_6H_4(CH_2)_2$	Cyclopentyl bromide	Diethyl cyclopentyl-[β-(m-methoxy-phenyl)ethyl]malonate	75	K	Toluene	412
	2-Cyclopentenyl chloride	Diethyl 2-cyclopentenyl-[β-(m-methoxy-phenyl)ethyl]malonate	08–70	K	Toluene	412
$p\text{-}CH_3C_6H_4(CH_2)_2$	$CH_3CCl=CHCH_2Cl$	$CH_3CCl=CHCH_2C(CO_2C_2H_5)_2$ $(CH_2)_2C_6H_4CH_3\text{-}p$	86	$NaOC_2H_5$	Ethanol	519

Note: References 577–1080 are on pp. 322–331.
‡ The halogen was not specified.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, $R'CH(CO_2R)_2$

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_{10}	C_1-C_{10}					
n-$C_{10}H_{21}$	CH₂—CH₂ (O epoxide)	CH₂CH₂C(C₁₀H₂₁-n)(CO₂C₂H₅) (O—CO)	ca. 70	$NaOC_2H_5$	Ethanol	282
	CH_2=$CHCH_2Br$	CH_2=$CHCH_2C(C_{10}H_{21}$-$n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	920, 713
	Cyclobutylmethyl bromide	Diethyl (cyclobutylmethyl)-n-decylmalonate	—	$NaOC_2H_5$	Ethanol	917
	β-(2-Cyclopentenyl)ethyl bromide	Diethyl n-decyl-1-[β-(2-cyclopentenyl)ethyl]-malonate	—	$NaOC_2H_5$	Ethanol	928
	n-$C_{10}H_{21}Br$	$(n$-$C_{10}H_{21})_2C(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	951
	n-$C_{12}H_{25}Br$-KI	n-$C_{12}H_{25}C(C_{10}H_{21}$-$n)(CO_2C_2H_5)_2$	70	$NaOC_2H_5$	Ethanol	70
	n-$C_{14}H_{29}I$	n-$C_{14}H_{29}C(C_{10}H_{21}$-$n)(CO_2C_2H_5)_2$	79	$NaOC_2H_5$	Ethanol	684
	n-$C_{16}H_{33}I$	n-$C_{16}H_{33}C(C_{10}H_{21}$-$n)(CO_2C_2H_5)_2$	84	$NaOC_2H_5$	Ethanol	135
$Br(CH_2)_{10}$	CH_3I	$Br(CH_2)_{10}C(CH_3)(CO_2C_2H_5)_2$	100	$NaOC_2H_5$	Ethanol	788
3,7-Dimethyloctyl	CH_2=$CHCH_2Br$	Diethyl allyl-(3,7-dimethyloctyl)malonate	—		—	743
Citronellyl(=$C_{10}H_{19}$)	Cyclopentyl bromide	Diethyl cyclopentyl(citronellyl)malonate	46	Na	Xylene	31
Geranyl(=$C_{10}H_{17}$)	n-$C_6H_{13}Br$	n-$C_6H_{13}C(C_{10}H_{17})(CO_2C_2H_5)_2$	67	Na	Xylene	31
	CH₂—CH₂ (O epoxide)	CH₂CH₂C(C₁₀H₁₇)CO₂C₂H₅ (O—CO)	ca. 70	$NaOC_2H_5$	Ethanol	282
	Cyclopentyl bromide	Diethyl cyclopentyl(geranyl)malonate	52	Na	Xylene	31
$C_6H_5(CH_2)_4$	C_2H_5Br	$C_6H_5(CH_2)_4C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	755
$C_6H_5CH_2SCH_2CH$ (CH_3)	CH_3I	$C_6H_5CH_2SCH_2OH(CH_3)C(CH_3)(CO_2C_2H_5)_2$	90	$NaOC_2H_5$	Ethanol	794
α-Naphthyl	C_2H_5I	Dimethyl ethyl-(α-naphthyl)malonate*	49	$NaOCH_3$	CH_3OH	376
β-Naphthyl	CH_2=$CHCH_2Br$	Diethyl allyl-(β-naphthyl)malonate	88	$NaOC_2H_5$	Ethanol	952

C_{11}

C_2–C_7

n-$C_{11}H_{23}$	$CH_2\!\!-\!\!CH_2$ (epoxide, bridging O)	$CH_2CH_2C(C_{11}H_{23}\text{-}n)(CO_2C_2H_5)$, ring $O\!\!-\!\!CO$	ca. 70	$NaOC_2H_5$	Ethanol	282
	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_{11}H_{23}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	920
	Cyclobutylmethyl bromide	Diethyl (cyclobutylmethyl)-n-undecyl-malonate	—	$NaOC_2H_5$	Ethanol	947
	β-(2-Cyclopentenyl)ethyl bromide	Diethyl n-undecyl-[β-(2-cyclopentenyl)-ethyl]malonate	—	$NaOC_2H_5$	Ethanol	928
	n-$C_{16}H_{33}I$	n-$C_{16}H_{33}C(C_{11}H_{23}\text{-}n)(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	135
n-$C_9H_{19}CH(CH_3)$	n-$C_{12}H_{25}Br$-NaI	n-$C_9H_{19}CH(CH_3)C(C_{12}H_{25}\text{-}n)(CO_2C_2H_5)_2$	50	Na	Xylene	70
$C_6H_5(CH_2)_5$	C_2H_5Br	$C_6H_5(CH_2)_5C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	755
2-p-Cymylmethyl	CH_3I	Diethyl methyl-(2-methyl-5-iso-propylbenzyl)malonate	76	Na	C_6H_6	808
	CH_3I	Diethyl methyl-(2-methyl-5-iso-propylbenzyl)malonate	76	$NaOC_2H_5$	Ethanol	418
1-Naphthylmethyl ($=C_{11}H_{13}$)	$CH_2=CHCH_2X$‡	Diethyl allyl-(1-naphthylmethyl)malonate	—	$NaOC_2H_5$	Toluene	512
	β-Bromomethylnaphthalene	Diethyl (1-naphthylmethyl)-(2-naphthylmethyl)malonate	—	—	—	945
2-Naphthylmethyl ($=C_{11}H_{13}$)	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_{11}H_{13})(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Toluene	513

C_{12}

n-$C_{12}H_{25}$¶¶	C_2H_5X¶¶	n-$C_{12}H_{25}C(C_2H_5)(CO_2C_2H_5)_2$	—	—	—	783
	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_{12}H_{25}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	920
	Cyclobutylmethyl bromide	Diethyl (cyclobutylmethyl)-n-dodecylmalonate	—	$NaOC_2H_5$	Ethanol	947
	β-(2 Cyclopentenyl)ethyl bromide	Diethyl n-dodecyl-[β-(2-cyclopentenyl)-ethyl]malonate	—	$NaOC_2H_5$	Ethanol	928
	n-$C_{16}H_{33}I$	n-$C_{16}H_{33}C(C_{12}H_{25}\text{-}n)(CO_2C_2H_5)_2$	88	$NaOC_2H_5$	Ethanol	135
$C_6H_5(CH_2)_6$	C_2H_5Br	$C_6H_5(CH_2)_6C(C_2H_5)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	755

Note: References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

‡ The halogen was not specified.

¶¶ The order of introduction of the alkyl groups was not stated.

TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
		$C_{12}H_{11}C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	839
β-1-Naphthylethyl ($C_{13}H_{13}$)	CH_3Br	$C_{12}H_{11}C(CH_3)(CO_2C_2H_5)_2$	96	$NaOC_2H_5$	Ethanol	953
	CH_3I	$C_{12}H_{11}C(C_2H_5)(CO_2C_2H_5)_2$	67	$NaOC_2H_5$	Ethanol	510
	C_2H_5Br	$C_{12}H_{11}C(CH_2CH=CH_2)(CO_2C_2H_5)_2$	47	$NaOC_2H_5$	Ethanol	546
	$CH_2=CHCH_2Br$	$C_{12}H_{11}C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	81	$NaOC_2H_5$	Ethanol	517
	$n\text{-}C_4H_9Br$	$CH_3CCl=CHCH_2C(C_{12}H_{11})(CO_2C_2H_5)_2$	88	$NaOC_2H_5$	Ethanol	817
	$CH_3CCl=CHCH_2Cl$	$CH_3CCl=CHCH_2C(C_{12}H_{11})(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	821
β-2-Naphthylethyl (=$C_{13}H_{13}$)	$CH_3CCl=CHCH_2Cl$	Diethyl methyl-(2-methyl-1-naphthylmethyl)malonate	—	Na	Xylene	
2-Methyl-1-naphthyl-methyl	CH_3I	Diethyl allyl-(4-methyl-1-naphthylmethyl)malonate	—	$NaOC_2H_5$	Toluene	514
1-Methyl-1-naphthyl-methyl	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_{13}H_{27}\text{-}n)(CO_2C_2H_5)_2$	>45	$NaOC_2H_5$	Ethanol	920
C_{13}	$CH_2=CHCH_2Br$	$(C_6H_5)_2CHC(CH(CO_2C_2H_5))(CO_2C_2H_5)_2$	39	Na	Ether	938
$n\text{-}C_{10}H_{21}$	CH_3I	$(C_6H_5)_2CHC(OH)_2C(CO_2C_2H_5)_2$	77	$NaOC_2H_5$	Ethanol	510
$(C_6H_5)_2CH$	$CH_2=CHCH_2Br$	$[(C_6H_5)_2CH]_2C(CO_2C_2H_5)_2$	22	Na	C_6H_6	150
	$(C_6H_5)_2CHBr$	$[(C_6H_5)_2CH]_2C(CO_2C_2H_5)_2$	89	Na	Toluene	224
	$(C_6H_5)_2CHBr$	$[(C_6H_5)_2CH]_2C(CO_2C_2H_5)_2$	25	BrMg salt*** of enolate	Ether	150, 054
	$(C_6H_5)_2CHBr$	$[(C_6H_5)_2CH]_2CH]_2C(CO_2C_2H_5)_2[(CO_2C_2H_5)_2]\dagger\dagger\dagger$	63	Na	C_6H_6	224
9-Fluorenyl	$(C_6H_5)_2CHBr$	$(p\text{-}CH_3C_6H_4)_2CHC[CH(C_6H_5)_2)_2](CO_2C_2H_5)_2$	—	Na	C_6H_6	150
β-(5-Methoxy-1-naphthyl)ethyl (=$C_{13}H_{13}O$)	$(p\text{-}CH_3C_6H_4)_2CHBr$	Diethyl allyl-(o-fluorenyl)malonate	70	—		510
	$CH_2=CHCH_2Br$	$CH_3CCl=CHCH_2C(C_{13}H_{13}O)(CO_2C_2H_5)_2$		$NaOC_2H_5$	Ethanol	520
	$CH_3CCl=CHCH_2Cl$					

C_{14}

	Halide	Product	Yield (%)	Condensing agent	Solvent	Ref.
n-$C_{11}H_{20}$	$CH_2=CHCH_2Br$	$CH_2=CHCH_2C(C_{11}H_{20}$-$n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	920
4-Isopropyl-1-naphthylmethyl	$CH_2=CHCH_2Br$	Diethyl allyl-(4-isopropyl-1-naphthylmethyl)malonate	—	$NaOC_2H_5$	Toluene	515
9-Phenanthryl ($=C_{14}H_9$)	n-C_3H_7I	$C_{14}H_9C(C_3H_7$-$n)(CO_2C_2H_5)_2$	61	$NaOC_2H_5$	Ethanol	955
	$CH_2=CHCH_2Br$	$C_{14}H_9C(CH_2CH=CH_2)(CO_2C_2H_5)_2$	82	$NaOC_2H_5$	Ethanol	955

C_{15}

	Halide	Product	Yield (%)	Condensing agent	Solvent	Ref.
$C_6H_5CH_2CH_2$·$(CO_2C_2H_5)CH$·$(CO_2C_2H_5)$	CH_3I	Tetramethyl α-methyl-δ-phenyl-butane-α,α,β,γ-tetracarboxylate	75	Na	C_6H_6	207
	CH_3I	Tetraethyl α-methyl-δ-phenyl-butane-α,α,β,γ-tetracarboxylate	75	$NaOC_2H_5$	Ethanol	207
††	CH_3I	$C_6H_5CH_2CH(CH_3)CONH_2$	—	Na	C_6H_6	207
††	CH_3I	$C_6H_5CH_2C(CH_3)(CO_2C_2H_5)_2$ $C_6H_5CH_2CH_2CH$——$CHC(CH_3)(CO_2C_2H_5)_2$ ($CO_2C_2H_5$, $CO_2C_2H_5$)	08	$NaOC_2H_5$	Ethanol	207
$(p$-$CH_3C_6H_4)_2CH$	$(C_6H_5)_2CHBr$	$(p$-$CH_3C_6H_4)_2CHCH[CH(C_6H_5)_2](CO_2C_2H_5)_2$	40	Na	C_6H_6	150
	$(C_6H_5)_2CHBr$	$(p$-$CH_3C_6H_4)_2CHC[CH(C_6H_5)_2]_2(CO_2C_2H_5)_2$	4	BrMg salt‡‡‡ of enolate	Ether	150
	$(p$-$CH_3C_6H_4)_2CHCl$	$[(p$-$CH_3C_6H_4)_2CH]_2C(CO_2C_2H_5)_2$	80	Na	C_6H_6	156
	$(p$-$CH_3C_6H_4)_2CHCl$	$[(p$-$CH_3C_6H_4)_2CH]_2C(CO_2C_2H_5)_2$	88	BrMg salt‡‡‡ of enolate	Ether	156
$C_6H_5COCH_2CH(C_6H_5)$	CH_3I	$C_6H_5COCH_2CH(C_6H_5)C(CH_3)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	154
$C_6H_5COCHBrCH(C_6H_5)$	None	H_5C_6CH——$CHCOC_6H_6$ $C(CO_2CH_3)_2$* (both isomers)	—	$Mg(OCH_3)_2$	CH_3OH	80, 956

low and high melting isomers

Note: References 577–1080 are on pp. 322–331.
* The dimethyl ester was used in this experiment.
†† The ester alkylated in this experiment was $C_6H_5CH_2C(CO_2C_2H_5)_2CH(CO_2C_2H_5)CH_2CO_2C_2H_5$.
*** The bromomagnesium salt of the enolate was derived from the addition of phenylmagnesium bromide to diethyl benzylidenemalonate.
††† Benzhydryl ethyl benzhydrylmalonate was used in this experiment.
‡‡‡ The bromomagnesium salt of the enolate was derived from addition of p-tolylmagnesium bromide to p-methylbenzylidenemalonate.
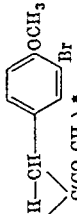
TABLE III—Continued

ALKYLATION OF MONOALKYLMALONIC ESTERS, R'CH(CO₂R)₂

(The diethyl ester was used unless otherwise indicated.)

R	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
p-BrC$_6$H$_4$COCHBr·CH(C$_6$H$_5$) (both isomers)	None	H$_5$C$_6$CH—CHCOC$_6$H$_4$Br-p C(CO$_2$CH$_3$)$_2$* (both isomers)	—	KOCOCH$_3$	CH$_3$OH	85
	None	H$_5$C$_6$CH—CHCOC$_6$H$_4$Br-p C(CO$_2$CH$_3$)$_2$* (both isomers)	—	Mg(OCH$_3$)$_2$	CH$_3$OH	85
C$_6$H$_5$COCHBrCH (C$_6$H$_4$NO$_2$-m) (both isomers)	None	m-O$_2$NH$_4$C$_6$CH—CHCOC$_6$H$_5$ C(CO$_2$CH$_3$)$_2$* (both isomers)	100	KOCOCH$_3$	CH$_3$OH	85
	None	m-O$_2$NH$_4$C$_6$CH—CHCOC$_6$H$_5$ C(CO$_2$CH$_3$)$_2$* (both isomers)	100	Mg(OCH$_3$)$_2$	CH$_3$OH	85

C_1–C_{16}

Substrate	Alkylating agent	Product	Yield %	Base	Solvent	Reference
C_{16}						
$n\text{-}C_{16}H_{33}$	CH_3I	$n\text{-}C_{16}H_{33}C(CH_3)(CO_2C_2H_5)_2$	—	Na	Xylene	670
	$(n\text{-}C_4H_9O)_2CO$	$n\text{-}C_{16}H_{33}C(C_4H_9\text{-}n)(CO_2C_4H_9)_2$§§§	83	$NaOC_4H_9\text{-}n$	$(n\text{-}C_4H_9O)_2CO$	330,800
	$C_6H_5CH_2Cl$	$n\text{-}C_{16}H_{33}C(CH_2C_6H_5)(CO_2C_2H_5)_2$	67	KOC_2H_5	$(C_2H_5O)_2CO$	44
	$C_6H_5CH_2Cl$	$n\text{-}C_{16}H_{33}C(CH_2C_6H_5)(CO_2C_4H_9)_2$§§§	67	$KOC_4H_9\text{-}n$	$(n\text{-}C_4H_9O)_2CO$	51,227
	$n\text{-}C_8H_{17}I$	$n\text{-}C_{16}H_{33}C(C_8H_{17}\text{-}n)(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	134
	$n\text{-}C_{16}H_{33}Br$	$(n\text{-}C_{16}H_{33})_2C(CO_2C_2H_5)_2$	64	Na	Xylene	679,957
	$n\text{-}C_{16}H_{33}Br$	$(n\text{-}C_{16}H_{33})_2C(CO_2C_2H_5)_2$	—	$NaOC_2H_5$	Ethanol	841
$C_6H_5COCHBrCH$ (with Br, OCH_3 substituted benzene)	None	$C_6H_5COCH\!-\!CH$ (OCH_3, Br)$C(CO_2CH_3)_2$*	53	$KOCOCH_3$	CH_3OH	958
C_7						
$n\text{-}C_{17}H_{35}$	CH_3I	$n\text{-}C_{17}H_{35}C(CH_3)(CO_2C_2H_5)_2$	—	Na	Toluene	400
C_{23}						
3-Decyltridecyl	CH_3I	Diethyl (3-decyltridecyl) methylmalonate	—	$NaOC_2H_5$	Ethanol	70

Note: References 577–1080 are on pp. 322–331.

* The dimethyl ester was used in this experiment.

§§§ The di-*n*-butyl ester was used in this experiment.

Starting material	Alkylating agent	Yield (%)	Condensing agent	Solvent	Product	References
$(C_2H_5O_2C)_2CH\text{-}CH(C_2H_5)OH(CO_2C_2H_5)_2$	Br_2 or I_2	—	Na	Ether	Tetraethyl 3-ethylcyclopropane-1,1,2,2-tetracarboxylate	87
	C_2H_5I	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(C_2H_5)CH(C_2H_5)\text{-}C(C_2H_5)(CO_2C_2H_5)_2$	87
$(C_2H_5O_2C)_2CHC(CH(CH_3)_2)\text{-}CH(CO_2C_2H_5)_2$	Br_2	—	Na	Ether	None	87
$(C_2H_5O_2C)_2CHCBrC(CH_3)_2\text{-}CH(CO_2C_2H_5)_2$	None	—	NH_3	CH_3OH	Tetraethyl 3,3-dimethylcyclopropane-1,1,2,2-tetracarboxylate	87
$(C_2H_5O_2C)_2CH\text{-}CH=C(CO_2C_2H_5)_2$	CH_3I	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(CH_3)CH=C(CO_2C_2H_5)_2$	221
	$C_6H_5CH_2Cl$	72–84	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(CH_2C_6H_5)\text{-}CH=C(CO_2C_2H_5)_2$	221, 231
	None	—	NH_3	CH_3OH	Tetraethyl 3-phenylcyclopropane-1,1,2,2-tetracarboxylate	87
$(C_2H_5O_2C)_2CBr\text{-}CH(C_6H_5)CH(CO_2C_2H_5)_2$	CH_3I	85	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(CH_3)CH(CH_2)_2\text{-}C(CH_3)(CO_2C_2H_5)_2$	002
$(C_2H_5O_2C)_2CH(CH_2)\text{-}CH(CO_2C_2H_5)_2$	CH_2I_2	—	$NaOC_2H_5$	Ethanol	Tetraethyl cyclopentane-1,1,3,3-tetracarboxylate $(C_2H_5O_2)_2C(C_2H_5)(CH_2)_2\text{-}CH(CO_2C_2H_5)_2$	301, 302
	C_2H_5I	65	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(C_2H_5)(CH_2)_2\text{-}CH(CO_2C_2H_5)_2$	600
$Br(CH_2)_2O(CH_2)_2Br$		17	$Mg(OC_2H_5)_2$	Ethanol	Tetraethyl octamethylene-oxide-4,4,7,7-tetracarboxylate	219
$(C_2H_5O_2C)_2CBr(CH_2)_2CBr(CH_2)_2CBr(CO_2C_2H_5)_2$		—	$NaOC_2H_5$	Ethanol	Cyclobutane-cis-1,2-dicarboxylic acid	261
$(C_2H_5O_2C)_2CH(CH_2)_2CH(CO_2C_2H_5)_2$	CH_3I	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(CH_3)(CH_2)_3\text{-}C(CH_3)(CO_2C_2H_5)_2$	303
	CH_2I_2	—	$NaOC_2H_5$	Ethanol	Tetraethyl cyclohexane-1,1,3,3-tetracarboxylate $(C_2H_5O_2)_2C(C_2H_5)(CH_2)_3\text{-}C(C_2H_5)(CO_2C_2H_5)_2$	299
	C_2H_5I	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(C_2H_5)(CH_2)_3\text{-}C(C_2H_5)(CO_2C_2H_5)_2$	303
	$n\text{-}C_3H_7I$	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(C_3H_7\text{-}n)(CH_2)_3\text{-}C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	303
	$i\text{-}C_3H_7I$	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(C_3H_7\text{-}i)(CH_2)_3\text{-}C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	303
	$i\text{-}C_4H_9I$	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(C_4H_9\text{-}i)(CH_2)_3\text{-}C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	303
	$C_6H_5CH_2Cl$	—	$NaOC_2H_5$	Ethanol	$(C_2H_5O_2)_2C(CH_2C_6H_5)(CH_2)_3\text{-}C(CH_2C_6H_5)(CO_2C_2H_5)_2$	303

Note: References 577–1080 are on pp. 322–331.

* The structure of the product is uncertain.

TABLE V

ALKYLATION OF ALKYLIDENEMALONIC ESTERS, $R=C(CO_2C_2H_5)_2$

R=	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$C_2H_5CH=$	$n\text{-}C_3H_7I$	$CH_3CH=CHC(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	51	$NaOC_2H_5$	Ethanol	28
	$i\text{-}C_3H_7I$	$CH_3CH=CHC(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	35	$NaOC_2H_5$	Ethanol	28
	$CH_2=CHCH_2Br$	$CH_3CH=CHC(CH_2CH=CH_2)(CO_2C_2H_5)_2$	76	$NaOC_2H_5$	Ethanol	215
	$n\text{-}C_4H_9I$	$CH_3CH=CHC(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	50	$NaOC_2H_5$	Ethanol	28
$(CH_3)_2C=$	$(CH_3)_2SO_4$	$CH_2=C(CH_3)C(CH_3)(CO_2C_2H_5)_2$	88	$NaNH_2$	Toluene	63
	$(C_2H_5)_2SO_4$	$CH_2=C(CH_3)C(C_2H_5)(CO_2C_2H_5)_2$	81	$NaNH_2$	Toluene	63
	$n\text{-}C_3H_7Br$	$CH_2=C(CH_3)C(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	50	$NaNH_2$	Toluene	63
	$i\text{-}C_3H_7I$	$CH_2=C(CH_3)C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	10	$NaNH_2$	Toluene	63
	$n\text{-}C_3H_7Br$	$CH_2=C(CH_3)C(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	82	$NaNH_2$	Toluene	63, 213
	$CH_2=CClCH_2Cl$	Structure not determined	Poor	$NaNH_2$	Toluene	64
	$CH_2=CBrCH_2Br$	Structure not determined	Poor	$NaNH_2$	Toluene	64
	$n\text{-}C_4H_9I$	$CH_2=C(CH_3)C(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	59	$NaNH_2$	Toluene	63
	$i\text{-}C_4H_9Br$	$CH_2=C(CH_3)C(C_4H_9\text{-}i)(CO_2C_2H_5)_2$	40	$NaNH_2$	Toluene	63
	$CH_3CH=CHCH_2Br$	$CH_2=C(CH_3)C(CH=CHCH_3)(CO_2C_2H_5)_2$	61	$NaNH_2$	Toluene	64
	$n\text{-}C_5H_{11}Br$	$CH_2=C(CH_3)C(C_5H_{11}\text{-}n)(CO_2C_2H_5)_2$	50	$NaNH_2$	Toluene	63
	$i\text{-}C_5H_{11}Br$	$CH_2=C(CH_3)C(C_5H_{11}\text{-}i)(CO_2C_2H_5)_2$	36	$NaNH_2$	Toluene	63
	$C_6H_5CH=CHCH_2Br$	$CH_2=C(CH_3)C(CH_2CH=CHC_6H_5)(CO_2C_2H_5)_2$	Poor	$NaNH_2$	Toluene	961
$n\text{-}C_3H_7CH=$	CH_3I	$C_2H_5CH=CHC(CH_3)(CO_2C_2H_5)_2$	80	$NaOC_2H_5$	Ethanol	28
	C_2H_5I	$C_2H_5CH=CHC(C_2H_5)(CO_2C_2H_5)_2$	75	$NaOC_2H_5$	Ethanol	212
	$(C_2H_5)_2SO_4$	$C_2H_5CH=CHC(C_2H_5)(CO_2C_2H_5)_2$	—	Na	Ether	28
	$n\text{-}C_3H_7Br$	$C_2H_5CH=CHC(C_3H_7\text{-}n)(CO_2C_2H_5)_2$	55	$NaOC_2H_5$	Ethanol	28
	$i\text{-}C_3H_7Br$	$C_2H_5CH=CHC(C_3H_7\text{-}i)(CO_2C_2H_5)_2$	67	$NaOC_2H_5$	Ethanol	28
	$CH_2=CHCH_2Br$	$C_2H_5CH=CHC(CH_2CH=CH_2)(CO_2C_2H_5)_2$	79	$NaOC_2H_5$	Ethanol	28
	$n\text{-}C_4H_9Br$	$C_2H_5CH=CHC(C_4H_9\text{-}n)(CO_2C_2H_5)_2$	59	$NaOC_2H_5$	Ethanol	28
	$sec\text{-}C_4H_9Br$	$C_2H_5CH=CHC(C_4H_9\text{-}sec)(CO_2C_2H_5)_2$	21	$NaOC_2H_5$	Ethanol	28

			Yield (%)	Base	Solvent	Ref.
CH₃C(OC₂H₅)=	C₂H₅X*	CH₂=C(OC₂H₅)C(C₂H₅)(CO₂C₂H₅)₂	20	NaOC₂H₅	Ethanol	203
	C₂H₅X*	CH₂=C(OC₂H₅)C(C₂H₅)(CO₂C₂H₅)₂	60	NaC₄H₉-t	t-C₄H₉OH	203
	n-C₃H₇X*	CH₂=C(OC₂H₅)C(C₃H₇-n)(CO₂C₂H₅)₂	72	NaOC₃H₇-i	i-C₃H₇OH	203
	CH₂=CHCH₂X*	CH₂=C(OC₂H₅)C(CH₂CH=CH₂)(CO₂C₂H₅)₂	59	NaOC₃H₇-i	i-C₃H₇OH	203
	n-C₄H₉X*	CH₂=C(OC₂H₅)C(C₄H₉-n)(CO₂C₂H₅)₂	85	NaOC₃H₇-i	i-C₃H₇OH	203
	i-C₅H₁₁X*	CH₂=C(OC₂H₅)C(C₅H₁₁-i)(CO₂C₂H₅)₂	79	NaOC₃H₇-i	i-C₃H₇OH	203
C₂H₅C(CH₃)=	(CH₃)₂SO₄	CH₃CH=C(OC₂H₅)C(CH₃)(CO₂C₂H₅)₂	76	NaNH₂	Toluene	237
	(C₂H₅)₂SO₄	CH₃CH=C(OC₂H₅)C(C₂H₅)(CO₂C₂H₅)₂	70	NaNH₂	Toluene	237
	n-C₃H₇Br	CH₃CH=C(OC₂H₅)C(C₃H₇-n)(CO₂C₂H₅)₂	65	NaNH₂	Toluene	237
	CH₂=CHCH₂Br	CH₃CH=C(OC₂H₅)C(CH₂CH=CH₂)(CO₂C₂H₅)₂	60	NaNH₂	Toluene	237
	n-C₄H₉Br	CH₃CH=C(OC₂H₅)C(C₄H₉-n)(CO₂C₂H₅)₂	67	NaNH₂	Toluene	237
i-C₃H₇CH=	C₂H₅I	(CH₃)₂C=CHC(C₂H₅)(CO₂C₂H₅)₂	40	NaOC₂H₅	Ethanol	28
n-C₄H₉CH=	C₂H₅Br	n-C₃H₇CH=CHC(C₂H₅)(CO₂C₂H₅)₂	60	NaOC₂H₅	Ethanol	28
	n-C₃H₇Br	n-C₃H₇CH=CHC(C₃H₇-n)(CO₂C₂H₅)₂	65	NaOC₂H₅	Ethanol	28
	i-C₃H₇I	n-C₃H₇CH=CHC(C₃H₇-i)(CO₂C₂H₅)₂	70	NaOC₂H₅	Ethanol	28
CH₃C(OC₃H₇-n)=	C₂H₅X*	CH₂=C(OC₃H₇-n)C(C₂H₅)(CO₂C₂H₅)₂	39	NaOC₃H₇-i	i-C₃H₇OH	203
i-C₄H₉CH=	CH₃I	i-C₃H₇CH=CHC(CH₃)(CO₂C₂H₅)₂	93	NaOC₂H₅	Ethanol	28
	C₂H₅I	i-C₃H₇CH=CHC(C₂H₅)(CO₂C₂H₅)₂	88	NaOC₂H₅	Ethanol	28
	n-C₃H₇Br	i-C₃H₇CH=CHC(C₃H₇-n)(CO₂C₂H₅)₂	86	NaOC₂H₅	Ethanol	28
	i-C₃H₇Br	i-C₃H₇CH=CHC(C₃H₇-i)(CO₂C₂H₅)₂	86	NaOC₂H₅	Ethanol	28
	CH₂=CHCH₂Br	i-C₃H₇CH=CHC(CH₂CH=CH₂)(CO₂C₂H₅)₂	92	NaOC₂H₅	Ethanol	215
	CH₃I	n-C₄H₉CH=CHC(CH₃)(CO₂C₂H₅)₂	82	NaOC₂H₅	Ethanol	28
	C₂H₅Br	n-C₃H₇CH=CHC(C₂H₅)(CO₂C₂H₅)₂	58	NaOC₂H₅	Ethanol	28
	C₂H₅X*	CH₂=C(OC₃H₇-n)C(C₂H₅)(CO₂C₂H₅)₂	24	NaOC₃H₇-i	i-C₃H₇OH	203
	C₂H₅X*	CH₂=C(OC₃H₇-i)C(C₂H₅)(CO₂C₂H₅)₂	55	NaOC₃H₇-i	i-C₃H₇OH	208

Note: References 577–1080 are on pp. 322–381.

* The halogen was not specified.

TABLE VI

ALKYLATION OF CYANOACETIC ESTERS, CH₂(CN)CO₂R

(The ethyl ester was used unless otherwise specified.)

Allylating Agent	Product	Yield, %	Base	Solvent	Reference
I₂	Triethyl 1,2,3-tricyanocyclopropano-1,2,3-tricarboxylate	—	Na	Ether	270
I₂	$C_2H_5O_2CCH(CN)CH(CN)CO_2C_2H_5$	—	Na	Ether	271, 272
C₁					
CH₃I	$CH_3CH(CN)CO_2C_2H_5$	—	Na	Ether	902
CH₃I	$\{CH_3CH(CN)CO_2C_2H_5$ $(CH_3)_2C(CN)CO_2C_2H_5$	72 12	NaOC₂H₅	Ethanol	568, 963
CH₃I	$CH_3CH(CN)CO_2C_2H_5$	80	NaOC₂H₅	Ether	185
CH₃I	$CH_3O_2CCH(CN)CH{=}C(CN)CO_2CH_3{*}$	—	NaOCH₃	CH₃OH	964
CHCl₃	$CH_3O_2CCH(CN)CH{=}C(CN)CO_2CH_3{*}$	—	NaOCH₃	CH₃OH	964, 580
CHCl₃	$C_2H_5O_2CCH(CN)CH{=}C(CN)CO_2C_2H_5$	70	NaOC₂H₅	Ethanol	965, 966, 967
CHI₃	$C_2H_5O_2CC(Na)(CN)CH{=}C(CN)CO_2C_2H_5$	60	NaOC₂H₅	Ethanol	964
CCl₄	$C_2H_5O_2CC(Na)(CN)CH{=}C(CN)CO_2C_2H_5$	41	NaOC₂H₅	Ethanol	589, 590, 591
CBr₄	$C_2H_5O_2CCH(CN)CH(CN)CO_2C_2H_5$	—	NaOC₂H₅	Ethanol	590, 591
CCl₃NO₂	$C_2H_5O_2CCH(CN)CH(CN)CO_2C_2H_5$	—	NaOC₂H₅	Ethanol	590, 591
C₂					
C₂H₅Br	$\{C_2H_5CH(CN)CO_2H$ $(C_2H_5)_2C(CN)CO_2CH_3{*}$	28 23	NaOC₂H₅	Ethanol	39
C₂H₅Br	$C_2H_5CH(CN)CO_2C_2H_5$, and $(C_2H_5)_2C(CN)CO_2C_2H_5$	—	NaOC₂H₅	Ethanol	968

C2H5Br	(C2H5)2C(CN)CO2C2H5	93†	NaOC2H5	Ethanol	169
C2H5I	C2H5CH(CN)CO2C2H5	—	Na	Ether	962
C2H5I	C2H5CH(CN)CO2C2H5	89	NaOC2H5	Ether	185
C2H5I	C2H5CH(CN)CO2C2H5	74	NaOC2H5	Ethanol	95, 963
C2H5I	(C2H5)2C(CN)CO2C2H5	30	NaOC2H5	Ethanol	95
(C2H5)2SO4	C2H5CH(CN)CO2C2H5	75	NaOC2H5	Ethanol	249
(C2H5)2SO4	(C2H5)2CH(CN)	60	NaOC2H5	Ethanol	249
CH3OCH2Cl	CH3OCH2CH(CN)CO2C2H5	—	Na	Ether	969
CH2ClCH2Cl	C2H5O2CCH(CN)(CH2)2CH(CN)CO2C2H5	—	—	—	970
CH2BrCH2Br	Ethyl 1-cyanocyclopropane-1-carboxylate, Ethyl 2-imino-3-cyanocyclopentane-1-carboxylate‡	>50	NaOC2H5	Ethanol	309, 479
CH2BrCH2Br	Ethyl 1-cyanocyclopropane-1-carboxylate, diethyl α,α′-dicyanoadipate, and ethyl 2-imino-3-cyanocyclopentane-1-carboxylate	—	NaOC2H5	Ethanol	310
C3					
n-C3H7Br	n-C3H7CH(CN)CO2C2H5, (n-C3H7)2C(CN)CO2C2H5	ca. 63, ca. 27	NaOC2H5	Ethanol	971, 972, 973
n-C3H7I	n-C3H7CH(CN)CO2C2H5, (n-C3H7)2C(CN)CO2C2H5	49, 20	NaOC2H5	Ethanol	38, 963
n-C3H7I	(n-C3H7)2C(CN)CO2C2H5	70	NaOC2H5	Ethanol	562
CH3SCH2CH2Cl·KI	CH3S(CH2)2CH(CN)CO2C2H5	54	NaOC2H5	Ethanol	288
i-C3H7Br	i-C3H7CH(CN)CO2C2H5	65	NaOC2H5	Ethanol	240
i-C3H7I	i-C3H7CH(CN)CO2C2H5, (i-C3H7)2C(CN)CO2C2H5	63	NaOC2H5	Ethanol	568, 225, 963
CH2=CHCH2I	CH2=CHCH2CH(CN)CO2C2H5	5, —	Na	Ether	962, 963

Note: References 577–1080 are on pp. 322–331.
* The methyl ester was used in this experiment.
‡ The reactants were added in inverse order.
‡ When originally isolated this product was formulated as ethyl α,δ-dicyanovalerate. It was later identified as the cyclo-pentane derivative indicated (ref. 712).

TABLE VI—*Continued*

ALKYLATION OF CYANOACETIC ESTERS, $CH_2(CN)CO_2R$

(The ethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
CH_3COCH_2Cl	$CH_3COCH_2CH(CN)CO_2CH_3$*	—	$NaOCH_3$	CH_3OH	123
CH_3COCH_2Cl	$CH_3COCH_2CH(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ether	123
$NC(CH_2)_2OSO_2C_6H_4CH_3$-$p$	$[NC(CH_2)_2]_2C(CN)CO_2C_2H_5$	86	$NaOC_2H_5$	Ethanol	102
$ClCH_2CO_2CH_3$	$ClH_2CCH_2CH(CN)CO_2CH_3$* and $(CH_3O_2CCH_2)_2C(CN)CO_2CH_3$*	—	$NaOCH_3$	CH_3OH	971
$Cl(CH_2)_3Br$	$Cl(CH_2)_3CH(CN)CO_2C_2H_5$	60	$NaOC_2H_5$	Ethanol	127
$Br(CH_2)_3Br$	$Br(CH_2)_3CH(CN)CO_2C_2H_5$	18	$NaOC_2H_5$	Ethanol	185
$Br(CH_2)_3Br$	$C_2H_5O_2CCH(CN)(CH_2)_3CH(CN)CO_2C_2H_5$, and ethyl 1-cyanocyclobutane-1-carboxylato	—	$NaOC_2H_5$	Ethanol	309
$H_2CCH{-}CH_2$ (with O)	H_2CCHCH_2CHCN ($O{-}CO$)	61	$NaOC_2H_5$	Ethanol	528
C_4					
n-C_4H_9Br	n-$C_4H_9CH(CN)CO_2C_2H_5$	76	$NaOC_2H_5$	Ethanol	288, 40
$C_2H_5O(CH_2)_2Br$	$C_2H_5O(CH_2)_2CH(CN)CO_2C_2H_5$	65	$NaOC_2H_5$	Ethanol	128
i-C_4H_9Br	i-$C_4H_9CH(CN)CO_2C_2H_5$	31	$NaOC_2H_5$	Ethanol	973, 975
i-C_4H_9Br	i-$C_4H_9CH(CN)CO_2C_2H_5$, and $(i$-$C_4H_9)_2C(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	472
i-C_4H_9I	$\{i$-$C_4H_9CH(CN)CO_2C_2H_5$ $\{(i$-$C_4H_9)_2C(CN)CO_2C_2H_5$	47	$NaOC_2H_5$	Ethanol	38, 963
i-C_4H_9I	$[i$-$C_4H_9CH(CN)CO_2H]$ $(i$-$C_4H_9)_2C(CN)CO_2C_4H_9$-i§	14 50	$NaOC_2H_5$,-i	i-C_4H_9OH	40
$C_2H_5CH(CH_3)Br$	$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	50	$NaOC_2H_5$	Ethanol	288

CH₃CH=CHCH₂Br	CH₃CH=CHCH₂CH(CN)CO₂C₂H₅	—	NaOC₂H₅	Ethanol	976
(CH₃)₂N(CH₂)₂Cl	(CH₃)₂N(CH₂)₂CH(CN)CO₂C₂H₅	39	Na	Ethanol	130
Cl(CH₂)₂O(CH₂)₂Cl	Ethyl 4-cyanotetrahydropyran-4-carboxylate	33	NaOC₂H₅	Ethanol	498, 497
(CH₃)₂C——CH₂ (O)	(CH₃)₂CCH₂CHCN —CO / O—CO	82	NaOC₂H₅	Ethanol	528
BrCH₂CH=CHCH₂Br	Ethyl 1-cyano-2-vinylcyclopropane-1-carboxylate, ethyl 2-imino-3-cyano-1-carboxylate, ethyl 2-imino-3-cyano-4-vinylcyclopentane-1-carboxylato and ethyl 2-imino-3-cyano-5-vinylcyclopentane-1-carboxylato	40	NaOC₂H₅	Ethanol	201
ClCH₂CO₂C₂H₅	C₂H₅O₂CCH₂CH(CN)CO₂C₂H₅	—	NaOC₂H₅	Ethanol	731, 974, 977
Cl₃CCO₂C₂H₅	C₂H₅O₂CCNa(CN)CH=C(CN)CO₂C₂H₅	—	NaOC₂H₅	Ethanol	964
C₅					
n-C₃H₇Br	n-C₃H₇CH(CN)CO₂C₂H₅	82	NaOC₂H₅	Ethanol	185
n-C₂H₅CH(CH₃)Br	n-C₂H₅CH(CH₃)CH(CN)CO₂C₂H₅	63	NaOC₂H₅	Ethanol	127
(C₂H₅)₂CHBr	(C₂H₅)₂CHCH(CN)CO₂C₂H₅	62	NaOC₂H₅	Ethanol	127, 238
i-C₅H₁₁Br	i-C₅H₁₁CH(CN)CO₂C₂H₅	76	NaOC₂H₅	Ethanol	973, 978
i-C₅H₁₁I	{ i-C₅H₁₁CH(CN)CO₂C₂H₅ (i-C₅H₁₁)₂C(CN)CO₂C₂H₅ }	— / 28	NaOC₂H₅	Ethanol	568
i-C₅H₁₁I	{ i-C₅H₁₁CH(CN)CO₂C₅H₁₁-i‖ and (i-C₅H₁₁)₂C(CN)CO₂C₅H₁₁-i }	—	NaOC₅H₁₁-i	i-C₅H₁₁OH	39
i-C₃H₇CH(CH₃)I	i-C₃H₇CH(CH₃)CH(CN)CO₂C₂H₅	45	NaOC₂H₅	Ethanol	470
CH₃CHBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)CH(CN)CO₂C₂H₅	70	NaOC₂H₅	Ethanol	167, 974
I(CH₂)₂CO₂C₂H₅	[C₂H₅O₂C(CH₂)₂]₂C(CN)CO₂C₂H₅	100	NaOC₂H₅	Ethanol	979

Note: References 577–1080 are on pp. 322–331.

* The methyl ester was used in this experiment.

§ The isobutyl ester was used in this experiment.

‖ The product also contained some of the ethyl ester.

TABLE VI—*Continued*

ALKYLATION OF CYANOACETIC ESTERS, $CH_2(CN)CO_2R$

(The ethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
Br·CH(CN)CO₂C₂H₅	$C_2H_5O_2C(NC)C$—$C(CN)CO_2C_2H_5$	67	Na	Ether	273
C₆					
n-C₄H₉Br	n-C₄H₉CH(CN)CO₂C₂H₅	70	NaOC₂H₅	Ethanol	469
n-C₃H₇CH(CH₃)Br	n-C₃H₇CH(CH₃)CH(CN)CO₂C₂H₅	50	NaOC₂H₅	Ethanol	127
i-C₃H₇CH(CH₃)Br	i-C₃H₇CH(CH₃)CH(CN)CO₂C₂H₅	60	NaOC₂H₅	Ethanol	470
(C₂H₅)₂CHCH₂Br	(C₂H₅)₂CHCH₂CH(CN)CO₂C₂H₅	50	NaOC₂H₅	Ethanol	469
(C₂H₅)₂N(CH₂)₂Cl	(C₂H₅)₂N(CH₂)₂CH(CN)CO₂C₂H₅	69	Na	CH₂(CN)CO₂C₂H₅·C₆H₆	130
C₂H₅CHBr(CO₂C₂H₅	C₂H₅O₂CCH(C₂H₅)CH(CN)CO₂C₂H₅	67	NaOC₂H₅	Ethanol	980
(CH₃)₂CBrCO₂C₂H₅	C₂H₅O₂CC(CH₃)₂CH(CN)CO₂C₂H₅	58	NaOC₂H₅	Ethanol	167, 981
Br(CH₂)₃CO₂C₂H₅	C₂H₅O₂C(CH₂)₃CH(CN)CO₂C₂H₅	62	NaOC₂H₅	Ethanol	185, 982
Cyclohexyl bromide	Ethyl cyclohexylcyanoacetate	23	NaOC₂H₅	Ethanol	469
Cyclohexyl iodide	Ethyl cyclohexylcyanoacetate	62	K₂CO₃	None	89
1,2-Dibromocyclohexane	{Ethyl 2-cyclohexenylcyanoacetate / Ethyl di-(2-cyclohexenyl)cyanoacetato	40 / —	—	—	150, 322
Cyclohexene oxide	3-Cyanohexahydro-2-benzofuranone	17	NaOC₂H₅	Ethanol	528
p-O₂NC₆H₄Cl	p-O₂NC₆H₄CH(CN)CO₂C₂H₅	—	NaOC₂H₅	Ethanol	325
2,4-Dinitrochlorobenzene	Ethyl (2,4-dinitrophenyl)cyanoacetate	90	NaOC₂H₅	Ethanol	325
Picryl chloride	Ethyl (2,4,6-trinitrophenyl)cyanoacetato	—	NaOC₂H₅	Ethanol	325
C₇					
n-C₇H₁₅Br	n-C₇H₁₅CH(CO₂H)₂	84	K₂CO₃	None	89
n-C₇H₁₅Br	n-C₇H₁₅CH(CN)CO₂C₂H₅	70	NaOC₂H₅	Ethanol	469
n-C₅H₁₁CH(CH₃)Br	n-C₅H₁₁CH(CH₃)CH(CN)CO₂C₂H₅	71	NaOC₂H₅	Ethanol	128

Alkylating agent	Product	Yield, %	Condensing agent	Solvent	References
$n\text{-}C_3H_7CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_3H_7\text{-}n)CH(CN)CO_2C_2H_5$	44–50	$NaOC_2H_5$	Ethanol	984
$CH_3CHBr(CH_2)_2CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_2CH(CH_3)CH(CN)CO_2C_2H_5$	—	—	—	283
$Br(CH_2)_4CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_4CH(CN)CO_2C_2H_5$	30	$NaOC_2H_5$	Ethanol	982
$I(CH_2)_4CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_4CH(CN)CO_2C_2H_5$	85	$NaOC_2H_5$	Ethanol	185
$Br(CH_2)_3CHBrCO_2C_2H_5$	Diethyl 1-cyanocyclopentano-1,2-dicarboxylate	89	$NaOC_2H_5$	Ethanol	629
$i\text{-}C_3H_7CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_3H_7\text{-}i)CH(CN)CO_2C_2H_5$	44–50	$NaOC_2H_5$	Ethanol	984
$C_2H_5OCH_2CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(CH_2OC_2H_5)CH(CN)CO_2C_2H_5$	28	Na	None	721
Cyclohexylmethyl iodide	Ethyl (cyclohexylmethyl)cyanoacetate	51	$NaOC_2H_5$	Ethanol	470
2-Methylcyclohexyl bromide	Ethyl (2-methylcyclohexyl)cyanoacetate	18	$NaOC_2H_5$	Ethanol	470
3-Methylcyclohexyl bromide	Ethyl (3-methylcyclohexyl)cyanoacetate	32	$NaOC_2H_5$	Ethanol	470
4-Methylcyclohexyl bromide	Ethyl (4-methylcyclohexyl)cyanoacetate	32	$NaOC_2H_5$	Ethanol	470
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(CN)CO_2C_2H_5$, and $(C_6H_5CH_2)_2C(CN)CO_2C_2H_5$	—	Na	None	95
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(CN)CO_2C_2H_5$	40	KOH	$(n\text{-}C_3H_7O)_2CHCH_3$	83
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(CN)CO_2C_2H_5$	30	KOH	$(n\text{-}C_4H_9O)_2CHCH_3$	83
$C_6H_5CH_2Cl$	$\{\,C_6H_5CH_2CH(CN)CO_2C_2H_5$; $(C_6H_5CH_2)_2C(CN)CO_2C_2H_5$; $(C_6H_5CH_2)_2C(CN)CO_2H\,\}$	14; Poor; Poor	$NaOCH_3$	CH_3OH	38
$C_6H_5CH_2Cl$	$\{\,(C_6H_5CH_2)_2C(CN)CO_2CH_3$ *; $(C_6H_5CH_2)_2C(CN)CO_2C_2H_5\,\}$	60	$NaOC_2H_5$	Ethanol	116, 95
$C_6H_5CH_2Cl$		Good	$NaOC_2H_5$	Ethanol	562
$o\text{-}ClC_6H_4CH_2Cl$	$o\text{-}ClC_6H_4CH_2CH(CN)CO_2C_2H_5$	42	$NaOC_2H_5$	Ethanol	128
$o\text{-}O_2NC_6H_4CH_2Cl$	$o\text{-}O_2NC_6H_4CH_2CH(CN)CO_2C_2H_5$ and $(o\text{-}O_2NC_6H_4CH_2)_2C(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	112
$C_6H_5CH_2Br$	$C_6H_5CH_2CH(CN)CO_2C_2H_5$	44	$NaOC_2H_5$	Ethanol	982
C_8					
$n\text{-}C_8H_{17}Br$	$n\text{-}C_8H_{17}CH(CN)CO_2C_2H_5$	75	$NaOC_2H_5$	Ethanol	469
$n\text{-}C_8H_{17}I$	$n\text{-}C_8H_{17}CH(CO_2H)_2$	95	K_2CO_3	None	89
$n\text{-}C_6H_{13}CH(CH_3)Br$	$n\text{-}C_6H_{13}CH(CH_3)CH(CN)CO_2C_2H_5$	63	$NaOC_2H_5$	Ethanol	128

Note: References 577–1080 are on pp. 322–331.

* The methyl ester was used in this experiment.

TABLE VI—Continued

ALKYLATION OF CYANOACETIC ESTERS, CH₂(CN)CO₂R

(The ethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
n-C₄H₉CH(C₂H₅)CH₂Br	n-C₄H₉CH(C₂H₅)CH₂CH(CN)CO₂C₂H₅	50	NaOC₂H₅	Ethanol	469
i-C₅H₁₁CH(CH₃)I	i-C₆H₁₃CH(CH₃)CH(CN)CO₂C₂H₅	81	NaOC₂H₅	Ethanol	750
i-C₄H₉CHBrCO₂C₂H₅	C₂H₅O₂CCH(C₄H₉-i)CH(CN)CO₂C₂H₅	65	NaOC₂H₅	Ethanol	985
Br(CH₂)₃CBr(CH₃)CO₂C₂H₅	Diethyl 2-cyano-1-methylcyclopentane-1,2-dicarboxylate	—	NaOC₂H₅	Ethanol	029
C₂H₅O₂CCH₂CHBrCO₂C₂H₅	Triethyl α-cyanotricarballylate	—	NaOC₂H₅	Ethanol	974
CH₃O₂CCHBr(CH₂)₂CHBr-CO₂CH₃ (low-melting form)	Trimethyl 2-cyanocyclo-pentane-1,2,3-tricarboxylate*	—	NaOCH₃	CH₃OH	753
CH₃O₂CCHBr(CH₂)₂CHBr-CO₂CH₃ (high-melting form)	Trimethyl 2-cyanocyclo-pentane-1,2,3-tricarboxylate*	—	NaOCH₃	CH₃OH	753
C₂H₅O₂CCHBrCHBr-CO₂C₂H₅ (meso form)	Triethyl 1-cyanocyclo-propane-1,2,3-tricarboxylate	85	NaOC₂H₅	Ethanol	175
C₂H₅O₂CCHBrCHBr-CO₂C₂H₅ (+, − form)	Triethyl 1-cyanocyclo-propane-1,2,3-tricarboxylate	—	NaOC₂H₅	Ethanol	175
β-Cyclohexylethyl bromide	Ethyl (β-cyclohexylethyl)cyanoacetate	70	NaOC₂H₅	Ethanol	127
C₆H₅(CH₂)₂Br	C₆H₅(CH₂)₂CH(CN)CO₂C₂H₅	78	NaOC₂H₅	Ethanol	469
C₆H₅(CH₂)₂Br	[C₆H₅(CH₂)₂]₂C(CN)CO₂C₂H₅	—	NaOC₂H₅	Ethanol	105
C₆H₅O(CH₂)₂Br	{ C₆H₅O(CH₂)₂CH(CN)CO₂C₂H₅	62	NaOC₂H₅	Ethanol	185
C₆H₅O(CH₂)₂Br	[C₆H₅O(CH₂)₂]₂C(CN)CO₂C₂H₅ }	32	NaOC₂H₅	Ethanol	185
p-ClC₆H₄O(CH₂)₂Br	p-ClC₆H₄O(CH₂)₂CH(CN)CO₂C₂H₅	52	NaOC₂H₅	Ethanol	128
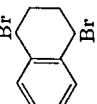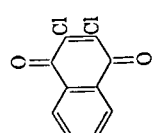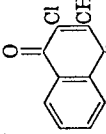
$o\text{-}CH_3C_6H_4CH_2Br$	$o\text{-}CH_3C_6H_4CH_2CH(CN)CO_2C_2H_5$	55	$NaOC_2H_5$	Ethanol	470
$m\text{-}CH_3C_6H_4CH_2Br$	$m\text{-}CH_3C_6H_4CH_2CH(CN)CO_2C_2H_5$	55	$NaOC_2H_5$	Ethanol	470
$p\text{-}CH_3C_6H_4CH_2Cl$	$p\text{-}CH_3C_6H_4CH_2CH(CN)CO_2C_2H_5$	48	$NaOC_2H_5$	Ethanol	470
$p\text{-}CH_3OC_6H_4CH_2Cl$	$p\text{-}CH_3OC_6H_4CH_2CH(CN)CO_2C_2H_5$	48	$NaOC_2H_5$	Ethanol	982
$C_6H_5COCH_2Br$	$C_6H_5COCH_2CH(CN)CO_2CH_3$* and $(C_6H_5COCH_2)_2C(CN)CO_2CH_3$*	—	$NaOCH_3$	CH_3OH	123
$C_6H_5COCH_2Br$	$C_6H_5COCH_2CH(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	123, 124
$C_6H_5COCH_2Br$	$(C_6H_5COCH_2)_2C(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	106
$C_6H_5COCH_2Br$	$C_6H_5COCH_2CH(CN)CO_2C_3H_7\text{-}n$¶	—	—	—	123
$o\text{-}NCC_6H_4CH_2Cl$	$o\text{-}NCC_6H_4CH_2CH(CN)CO_2C_2H_5$	Good	$NaOC_2H_5$	Ethanol	198
$o\text{-}NCC_6H_4CH_2Cl$	$(o\text{-}NCC_6H_4CH_2)_2C(CN)CO_2C_2H_5$	80	$NaOC_2H_5$	Ethanol	198, 111
(benzene ring with CH_2Br, CH_2Br)	(indane ring with $C(CN)CO_2C_2H_5$, CH_2, CH_2)	95	$NaOC_2H_5$	Ethanol-ether	185
C_9					
$n\text{-}C_9H_{19}Br$	$n\text{-}C_9H_{19}CH(CN)CO_2C_2H_5$	70	$NaOC_2H_5$	Ethanol	127
$C_2H_5O_2CCHBrCH_2\text{-}CHBrCO_2C_2H_5$	Triethyl 2-cyanocyclobutane-1,2,3-tricarboxylate	70	$NaOC_2H_5$	Ethanol	176
$C_6H_5(CH_2)_3Br$	$C_6H_5(CH_2)_3CH(CN)CO_2C_2H_5$	68	$NaOC_2H_5$	Ethanol	469
$C_6H_5O(CH_2)_3Br$	$C_6H_5O(CH_2)_3CH(CN)CO_2C_2H_5$	40	$NaOC_2H_5$	Ethanol	982
$o\text{-}BrC_6H_4O(CH_2)_3Br$	$o\text{-}BrC_6H_4O(CH_2)_3CH(CN)CO_2C_2H_5$	45	$NaOC_2H_5$	Ethanol	471
$2,4\text{-}Cl_2C_6H_3O(CH_2)_3Br$	$2,4\text{-}Cl_2C_6H_3O(CH_2)_3CH(CN)CO_2C_2H_5$	38	$NaOC_2H_5$	Ethanol	471
$p\text{-}BrC_6H_4O(CH_2)_3Br$	$p\text{-}BrC_6H_4O(CH_2)_3CH(CN)CO_2C_2H_5$	65	$NaOC_2H_5$	Ethanol	128
$C_6H_5CH_2S(CH_2)_2Cl\cdot KI$	$C_6H_5CH_2S(CH_2)_2CH(CN)CO_2C_2H_5$	49	$NaOC_2H_5$	Ethanol	288
$p\text{-}C_2H_5C_6H_4CH_2Cl$	$p\text{-}C_2H_5C_6H_4CH_2CH(CN)CO_2C_2H_5$	50	$NaOC_2H_5$	Ethanol	470
$p\text{-}CH_3C_6H_4O(CH_2)_2Cl$	$p\text{-}CH_3C_6H_4O(CH_2)_2CH(CN)CO_2C_2H_5$	62	$NaOC_2H_5$	Ethanol	128
1-Bromoindane	Ethyl 1-indanylcyanoacetate	20	$NaOC_2H_5$	Ethanol	127

Note: References 577–1080 are on pp. 322–331.

* The methyl ester was used in this experiment.

¶ The n-propyl ester was used in this experiment.

TABLE VI—*Continued*

ALKYLATION OF CYANOACETIC ESTERS, $CH_2(CN)CO_2R$

(The ethyl ester was used unless otherwise specified.)

Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
2,3-Dichloroindenone	Ethyl chloroindenonylcyanoacetate**	—	—	—	986
2,3-Dibromoindenone	Ethyl bromoindenonylcyanoacetate** and diethyl indenone-2,3-dicyanoacetate	—	—	—	986
C_{10}					
$n\text{-}C_{10}H_{21}Br$	$n\text{-}C_{10}H_{21}CH(CN)CO_2C_2H_5$	65	$NaOC_2H_5$	Ethanol	469
$C_2H_5O_2CCHBr(CH_2)_3CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_3CH(CO_2C_2H_5)\text{-}CH(CN)CO_2C_2H_5$	55	$NaOC_2H_5$	Ethanol	787
$m\text{-}CH_3C_6H_4O(CH_2)_3Br$	$[m\text{-}CH_3C_6H_4O(CH_2)_3]_2C(CN)CO_2C_2H_5$	57	$NaOC_2H_5$	Ethanol	471
$p\text{-}CH_3C_6H_4O(CH_2)_3Br$	$p\text{-}CH_3C_6H_4O(CH_2)_3CH(CN)CO_2C_2H_5$	74	$NaOC_2H_5$	Ethanol	129
$p\text{-}C_2H_5C_6H_4O(CH_2)_2Br$	$p\text{-}C_2H_5C_6H_4O(CH_2)_2CH(CN)CO_2C_2H_5$	60	$NaOC_2H_5$	Ethanol	128

(dibromotetralin alkylating agent, Br, Br) → $CH(CN)CO_2C_2H_5\dagger\dagger$ (dihydronaphthalene product)   —   —   —   150

(dichloronaphthoquinone, Cl, Cl) → chloronaphthoquinone $CH(CN)CO_2C_2H_5$ and bis $CH(CN)CO_2C_2H_5$ / $CH(CN)CO_2C_2H_5$ naphthoquinone   —   —   —   986

C_{11}

n-$C_{11}H_{23}I$	n-$C_{11}H_{23}CH(CO_2H)_2$	81	K_2CO_3	None	89
m-$C_2H_5C_6H_4O(CH_2)_3Br$	$[m$-$C_2H_5C_6H_4O(CH_2)_3]_2C(CN)CO_2C_2H_5$	40	$NaOC_2H_5$	Ethanol	471
p-$C_2H_5C_6H_4O(CH_2)_3Br$	p-$C_2H_5C_6H_4O(CH_2)_3CH(CN)CO_2C_2H_5$	70	$NaOC_2H_5$	Ethanol	128
1-Chloromethylnaphthalene	Ethyl (1-naphthylmethyl)cyanoacetate	45	$NaOC_2H_5$	Ethanol	469

C_{12}

n-$C_{12}H_{25}Br$	n-$C_{12}H_{25}CH(CN)CO_2C_2H_5$	75	$NaOC_2H_5$	Ethanol	128

C_{16}–C_{19}

n-$C_{16}H_{35}I$	n-$C_{16}H_{33}CH(CO_2H)_2$	90	K_2CO_3	None	89
n-$C_{16}H_{33}Br$	n-$C_{16}H_{33}CH(CN)CO_2C_2H_5$	75	$NaOC_2H_5$	Ethanol	127
$(C_6H_5)_3CBr$	$(C_6H_5)_3CCH(CN)CO_2C_2H_5$	Poor	$NaOC_2H_5$	Ethanol	987

Note: References 577–1080 are on pp. 322–331.

** The structure of the product was not determined.

†† The position of the double bond was not stated.

TABLE VII

ALKYLATION OF BROMO-, ACETAMIDO-, AND PHENYLACETAMIDO-CYANOACETIC ESTERS, $XCH(CN)CO_2R$

(The ethyl ester was used unless otherwise indicated.)

X	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
Br	None	Triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate	25	Aniline	Ether	273
	None	Triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate	60	Na	Ether	273
CH_3CONH	CH_3I	$CH_3CONHC(CH_3)(CN)CO_2C_2H_5$	71	$NaOC_2H_5$	Ethanol	232
	C_2H_5Br	$CH_3CONHC(C_2H_5)(CN)CO_2C_2H_5$	85	$NaOC_2H_5$	Ethanol	232
	$n\text{-}C_3H_7Br$	$CH_3CONHC(C_3H_7\text{-}n)(CN)CO_2C_2H_5$	70	$NaOC_2H_5$	Ethanol	232
	$CH_3S(CH_2)_2Cl$	$CH_3S(CH_2)_2C(NHCOCH_3)(CN)CO_2C_2H_5$	60	$NaOC_2H_5$	Ethanol	241
	$i\text{-}C_3H_7Br$	$CH_3CONHC(C_3H_7\text{-}i)(CN)CO_2C_2H_5$	66	$NaOC_2H_5$	Ethanol	241
	$CH_2{=}CHCH_2Br$	$CH_3CONHC(CH_2CH{=}CH_2)(CN)CO_2C_2H_5$	82	$NaOC_2H_5$	Ethanol	232
	$n\text{-}C_4H_9I$	$CH_3CONHC(C_4H_9\text{-}n)(CN)CO_2C_2H_5$	78	$NaOC_2H_5$	Ethanol	232
	$i\text{-}C_4H_9Br$	$CH_3CONHC(C_4H_9\text{-}i)(CN)CO_2C_2H_5$	65	$NaOC_2H_5$	Ethanol	241, 232
	$CH_2{=}C(CH_3)CH_2Cl$	$CH_3CONHC[CH_2C(CH_3){=}CH_2](CN)CO_2C_2H_5$	82	$NaOC_2H_5$	Ethanol	232
	4-Chloro-methylimidazole hydrochloride	Ethyl α-acetamido-α-cyano-β-(4-imidazolyl)propionate	60	$NaOC_2H_5$	Ethanol	241
	$n\text{-}C_5H_{11}Br$	$CH_3CONHC(C_5H_{11}\text{-}n)(CN)CO_2C_2H_5$	57	$NaOC_2H_5$	Ethanol	232
	$n\text{-}C_6H_{13}I$	$CH_3CONHC(C_6H_{13}\text{-}n)(CN)CO_2C_2H_5$	81	$NaOC_2H_5$	Ethanol	232
	$n\text{-}C_7H_{15}Br$	$CH_3CONHC(C_7H_{15}\text{-}n)(CN)CO_2C_2H_5$	65	$NaOC_2H_5$	Ethanol	232
	$C_6H_5CH_2Cl$	$CH_3CONHC(CH_2C_6H_5)(CN)CO_2C_2H_5$	83	$NaOC_2H_5$	Ethanol	241
	$n\text{-}C_8H_{17}I$	$CH_3CONHC(C_8H_{17}\text{-}n)(CN)CO_2C_2H_5$	81	$NaOC_2H_5$	Ethanol	232
	$p\text{-}CH_3OC_6H_4CH_2Br$	$p\text{-}CH_3OC_6H_4CH_2C(NHCOCH_3)(CN)CO_2C_2H_5$*	96	$NaOC_2H_5$	Ethanol	242
	$n\text{-}C_9H_{19}Br$	$CH_3CONHC(C_9H_{19}\text{-}n)(CN)CO_2C_2H_5$	32	$NaOC_2H_5$	Ethanol	232

γ-Phthalimidopropyl bromide	$C_8H_4O_2N(CH_2)_3C(NHCOCH_3)(CN)CO_2C_2H_5$ *	75	$NaOC_2H_5$	Ethanol	242
δ-Phthalimidobutyl iodide	$C_8H_4O_2N(CH_2)_4C(NHCOCH_3)(CN)CO_2C_2H_5$ *	80	$NaOC_2H_5$	Ethanol	242
$CH_3S(CH_2)_2Cl$	$CH_3S(CH_2)_2C(C_8H_8ON)(CN)CO_2CH_3$†	ca. 76	$NaOC_2H_5$	Ethanol	243
$C_6H_5CH_2CONH$ ($=C_8H_8ON$)					
i-C_3H_7I	i-$C_3H_7C(C_8H_8ON)(CN)CO_2CH_3$†	—	$NaOC_2H_5$	Ethanol	243
i-C_4H_9I	i-$C_4H_9C(C_8H_8ON)(CN)CO_2CH_3$†	—	$NaOC_2H_5$	Ethanol	243
$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_8H_8ON)(CN)CO_2CH_3$†	—	$NaOCH_3$	CH_3OH	244
$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_8H_8ON)(CN)CO_2CH_3$†	—	$NaOC_2H_5$	Ethanol	243
p-$CH_3OC_6H_4CH_2Cl$	p-$CH_3OC_6H_4CH_2C(C_8H_8ON)(CN)CO_2CH_3$†	—	$NaOCH_3$	CH_3OH	244
p-$CH_3OC_6H_4CH_2Cl$	p-$CH_3OC_6H_4CH_2C(C_8H_8ON)(CN)CO_2CH_3$†	—	$NaOC_2H_5$	Ethanol	243
p-$CH_3C_6H_4SO_2$-$C_6H_4CH_2Br$-p	p-$CH_3C_6H_4SO_2C_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$†	50	$NaOC_2H_5$	Ethanol	245
p-$CH_3OC_6H_4SO_2$-$C_6H_4CH_2Br$-p	p-$CH_3OC_6H_4SO_2C_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$†	poor	Na	C_6H_6	245
p-$CH_3OC_6H_4SO_2$-$C_6H_4CH_2Br$-p	p-$CH_3OC_6H_4SO_2C_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$†	80	$NaOC_2H_5$	Ethanol	245
p-$BrCH_2C_6H_4SO_2$-$C_6H_4CH_2Br$-p	$O_2S[C_6H_4CH_2C(C_8H_8ON)(CN)CO_2CH_3$-$p]_2$†	50	$NaOC_2H_5$	Ethanol	245
p-$CH_3OC_6H_4COC_6H_4$-CH_2Br-p	p-$CH_3OC_6H_4COC_6H_4CH_2$-$C(C_8H_8ON)(CN)CO_2CH_3$†	78	$NaOC_2H_5$	Ethanol	245

* The ethyl acetamidocyanoacetate used contained radioactive carbon.

† The methyl ester was used in this experiment.

TABLE VIII

Alkylation of Monoalkylcyanoacetic Esters, $RCH(CN)CO_2R'$

(The ethyl ester was used unless otherwise indicated.)

R	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_1						
CH_3	CH_2I_2	$C_2H_5O_2CC(CH_3)(CN)CH_2\cdot C(CH_3)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	988
	$(CH_3)_2CBrCO_2C_2H_5$	$C_2H_5O_2CC(CH_3)_2C(CH_3)(CN)\cdot CO_2C_2H_5$	ca. 100	$NaOC_2H_5$	Ethanol	989, 164
C_2						
C_2H_5	$i\text{-}C_3H_7I$	$i\text{-}C_3H_7C(C_2H_5)(CN)CO_2C_2H_5$	20	$NaOC_2H_5$	Ethanol	145
C_3						
$n\text{-}C_3H_7$	C_2H_5I	$n\text{-}C_3H_7C(C_2H_5)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	562
	$CH_2{=}CHCH_2I$	$CH_2{=}CHCH_2C(C_3H_7\text{-}n)(CN)\cdot CO_2C_2H_5$	83	$NaOC_2H_5$	Ethanol	971, 972
$i\text{-}C_3H_7$	C_2H_5I	$i\text{-}C_3H_7C(C_2H_5)(CN)CO_2C_2H_5$	86	$NaOC_2H_5$	Ethanol	239
	$n\text{-}C_3H_7Br$	$i\text{-}C_3H_7C(C_3H_7\text{-}n)(CN)CO_2C_2H_5$	76	$NaOC_2H_5$	Ethanol	240
	$i\text{-}C_3H_7I$	$(i\text{-}C_3H_7)_2C(CN)CO_2C_2H_5$	95	$NaOC_2H_5$	Ethanol	225
C_4						
$n\text{-}C_4H_9$	$i\text{-}C_3H_7Br$	$n\text{-}C_4H_9C(C_3H_7\text{-}i)(CN)CO_2C_2H_5$	87	$NaOC_2H_5$	Ethanol	575
$i\text{-}C_4H_9$	C_2H_5Br	$i\text{-}C_4H_9C(C_2H_5)(CN)CO_2C_3H_7\text{-}n*$	78	$NaOC_3H_7\text{-}n$	$(n\text{-}C_3H_7O)_2CO$	44, 51, 227
	$i\text{-}C_4H_9I$	$(i\text{-}C_4H_9)_2C(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	973
$sec\text{-}C_4H_9$	$n\text{-}C_3H_7Br$	$sec\text{-}C_4H_9C(C_3H_7\text{-}n)(CN)CO_2C_2H_5$	73	$NaOC_2H_5$	Ethanol	214
	$sec\text{-}C_4H_9Br$	$(sec\text{-}C_4H_9)_2C(CN)CO_2C_2H_5$	50	$NaOC_2H_5$	Ethanol	575
$CH_3CH{=}CHCH_2$	$CH_2{=}CHCH_2Br$	$CH_3CH{=}CHCH_2\cdot C(CH_2CH{=}CH_2)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	976
$CH_3O_2CCH_2$	CH_3I	$CH_3O_2CCH_2C(CH_3)(CN)CO_2CH_3\dagger$	—	$NaOCH_3$	CH_3OH	974
$C_2H_5O_2CCH_2$	C_2H_5I	$C_2H_5O_2CCH_2C(C_2H_5)(CN)CO_2C_2H_5$	79	$NaOC_2H_5$	Ethanol	980, 974
	$n\text{-}C_3H_7I$	$C_2H_5O_2CCH_2C(C_3H_7\text{-}n)(CN)\cdot CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	974

Substrate	Halide	Product	Yield %	Condensing agent	Solvent	References
— CH_2=$CHCH_2$	$ClCH_2CO_2C_2H_5$	$(C_2H_5O_2CCH_2)_2C(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	977
	$CH_3CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(CH_3)C(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	974
(=C_4H_3S)	$C_6H_5CH_2Cl$	$CH_2CO_2C_2H_5$ $C_2H_5O_2CCH_2C(CH_2C_6H_5)(CN)$ $CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	974
	$ClCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(C_4H_3S)(CN)$ $CO_2C_2H_5$	60	K_2CO_3	$(CH_3)_2CO$	88
	2-Cyclohexenyl bromide	Ethyl 2-thienyl-(2-cyclohexenyl)-cyanoacetate	67	$NaOC_2H_5$	Ethanol	187
C_5						
$(C_2H_5)_2CH$	C_2H_5Br	$(C_2H_5)_2CHC(C_2H_5)(CN)CO_2C_2H_5$	Good	$NaOC_2H_5$	Ethanol	238, 983
$C_2H_5O_2CCH_2C(=NH)$	ICH_2CN	HN=C NH—C=$C(CN)CO_2C_2H_5$ CH_2—$CHCO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	990
$CH_3CH(CO_2C_2H_5)$	CH_3I	$C_2H_5O_2CCH(CH_3)$-$C(CH_3)(CN)CO_2C_2H_5$	75	$NaOC_2H_5$	Ethanol	167, 981
	n-C_3H_7I	$C_2H_5O_2CCH(CH_3)$-$C(C_3H_7$-$n)(CN)CO_2C_2H_5$	81	$NaOC_2H_5$	Ethanol	985
	i-C_4H_9X‡	$C_2H_5O_2CCH(CH_3)$-$C(C_4H_9$-$i)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	985
C_6						
$(CH_3)_2C(CO_2C_2H_5)$	CH_3I	$C_2H_5O_2CC(CH_3)_2$-$C(CH_3)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	981
2-Cyclohexenyl (=C_6H_9)	CH_3I	$C_6H_5C(CH_3)C(CH_3)(CN)CO_2C_2H_5$	85	$NaOC_2H_5$	Ethanol	290

Note: References 577–1080 are on pp. 322–331.

* The *n*-propyl ester was used in this experiment.

† The methyl ester was used in this experiment.

‡ The halogen was not specified.

TABLE VIII—Continued

ALKYLATION OF MONOALKYLCYANOACETIC ESTERS, RCH(CN)CO₂R'

(The ethyl ester was used unless otherwise indicated.)

R	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
2-Cyclohexenyl (=C₆H₉) (Cont.)	C₂H₅Br·KI	C₆H₉C(C₂H₅)(CN)CO₂C₂H₅	83–87	NaOC₂H₅	Ethanol	290, 991
	C₂H₅Br	C₆H₉C(C₂H₅)(CN)CO₂C₂H₅	90§	NaOC₂H₅	Ethanol	169
	n-C₃H₇Br·KI	C₆H₉C(C₃H₇-n)(CN)CO₂C₂H₅	62	NaOC₂H₅	Ethanol	290
	n-C₄H₉Br·KI	C₆H₉C(C₄H₉-n)(CN)CO₂C₂H₅	73	NaOC₂H₅	Ethanol	290, 226
	n-C₄H₉Br·KI	C₆H₉C(C₄H₉-n)(CN)CO₂C₂H₅	49	NaOC₂H₅	Ethanol	290
	n-C₆H₁₃Br·KI	C₆H₉C(C₆H₁₃-n)(CN)CO₂C₂H₅	54	KOH	CH₃CH(OC₃H₇-n)₂	81, 83
	C₆H₅CH₂Cl	C₆H₉C(CH₂C₆H₅)(CN)CO₂C₂H₅	77	NaOC₂H₅	Ethanol	992
C₆H₅	CH₃I	C₆H₅C(CH₃)(CN)CO₂C₂H₅	88	KOH	1-Butoxy-2-ethoxyethane	81
	ClCH₂CN	NCCH₂C(C₆H₅)(CN)CO₂C₂H₅	88	KOH	CH₃CH(OC₄H₉-n)₂	83
	ClCH₂CN	NCCH₂C(C₆H₅)(CN)CO₂C₂H₅	91	NaNH₂	Toluene	188
	CH₂BrCH₂Br	Br(CH₂)₂C(C₆H₅)(CN)CO₂C₂H₅	—	NaOC₂H₅	Ethanol	188
	Cl(CH₂)₂CN	NC(CH₂)₂C(C₆H₅)(CN)CO₂C₂H₅	63	NaNH₂	Toluene	188
	Cl(CH₂)₃CN	Cl(CH₂)₃C(C₆H₅)(CN)CO₂C₂H₅	78	NaOC₂H₅	Ethanol	502, 188
	ClCH₂CO₂C₂H₅	C₂H₅O₂CCH₂C(C₆H₅)(CN)CO₂C₂H₅	81	NaOC₂H₅	Ethanol	993
	CH₃CHBrCO₂C₂H₅	C₂H₅O₂CCH(CH₃)-C(C₆H₅)(CN)CO₂C₂H₅	60	NaOC₂H₅	Ethanol	993
	Cl(CH₂)₂CO₂C₂H₅	C₂H₅O₂C(CH₂)₂-C(C₆H₅)(CN)CO₂C₂H₅	82	NaOC₂H₅	Ethanol	993
	(CH₃)₂CBrCO₂C₂H₅	C₂H₅O₂CC(CH₃)₂-C(C₆H₅)(CN)CO₂C₂H₅	53	NaOC₂H₅	Ethanol	993
	C₆H₅CH₂Cl	C₆H₅CH₂C(C₆H₅)(CN)CO₂C₂H₅	88	NaOC₂H₅	Ethanol	333
	C₆H₅CH₂N(CH₃)(CH₂)₂Cl	C₆H₅CH₂N(CH₃)(CH₂)₂-C(C₆H₅)(CN)CO₂C₂H₅	87	Na	Ether-toluene	188
	C₆H₅CH₂N(CH₃)(CH₂)₃Cl	C₆H₅CH₂N(CH₃)(CH₂)₃-C(C₆H₅)(CN)CO₂C₂H₅	76	NaNH₂	Toluene	188

C7

$C_2H_5O_2C(CH_2)_2CH(CH_3)$	CH_3I	$C_2H_5O_2C(CH_2)_2CH(CH_3)$-$C(CH_3)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	283
n-$C_3H_7CH_2CH(CO_2C_2H_5)$	n-C_3H_7I	$C_2H_5O_2CCH(C_3H_7$-$n)$-$C(C_3H_7$-$n)(CN)CO_2C_2H_5$	78	$NaOC_2H_5$	Ethanol	984
i-$C_3H_7CH(CO_2C_2H_5)$	n-C_3H_7I	$C_2H_5O_2CCH(C_3H_7$-$i)$-$C(C_3H_7$-$n)(CN)CO_2C_2H_5$	82	$NaOC_2H_5$	Ethanol	984
	i-C_3H_7I	$C_2H_5O_2CCH(C_3H_7$-$i)$-$C(C_3H_7$-$i)(CN)CO_2C_2H_5$	70	$NaOC_2H_5$	Ethanol	984
$C_6H_5CH_2$	$C_6H_5CH_2N(CH_3)$-$(CH_2)_2Cl$	$C_6H_5CH_2N(CH_3)(CH_2)_3$-$C(CH_3,C_6H_5)(CN)CO_2C_2H_5$	—	$NaNH_2$	Toluene	188
o-$CH_3C_6H_4$	$C_6H_5CH_2N(CH_3)$-$(CH_2)_2Cl$	$C_6H_5CH_2N(CH_3)(CH_2)_3$-$C(CH_3,C_6H_4$-$o)(CN)CO_2C_2H_5$	65	$NaNH_2$	Toluene	188
p-$CH_3C_6H_4$	C_2H_5Br	p-$CH_3C_6H_4C(C_2H_5)(CN)CO_2C_2H_5$	60	$NaOC_2H_5$	$(C_2H_5O)_2CO$	44, 227

C8

i-$C_6H_{13}CH(CH_3)$	$C_2H_5O(CH_2)_2I$	$C_2H_5O(CH_2)_2C(CN)CO_2C_2H_5$ with i-$C_6H_{13}CHCH_3$	80	K	Xylene	750
i-$C_4H_9CH(CO_2C_2H_5)$	i-C_4H_9Br	$C_2H_5O_2CCH(C_4H_9$-$i)(CN)CO_2C_2H_5$ with $C(C_4H_9$-$i)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	985
$C_6H_5COCH_2$	CH_3I	$C_6H_5COCH_2C(CH_3)(CN)CO_2CH_3$ *	—	$NaOCH_3$	CH_3OH	123
	C_2H_5I	$C_6H_5COCH_2C(C_2H_5)(CN)CO_2C_2H_5$	—	$NaOC_2H_5$	Ethanol	123
	$C_6H_5CH_2Cl$	$C_6H_5COCH_2C(CH_2C_6H_5)(CN)$-$CO_2CH_3$ *	—	$NaOCH_3$	CH_3OH	123

C9

1-Indanyl	n-C_3H_7I	Ethyl 1-indanyl-(n-propyl)cyano-acetate	41	$NaOC_2H_5$	Ethanol	217

C13

$(C_6H_5)_2CH$	$(C_6H_5)_2CHCl$	$[(C_6H_5)_2CH]_2C(CN)CO_2C_2H_5$	—	BrMg enolate‖	Ether	994
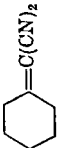
Note: References 577–1080 are on pp. 322–331.

* The methyl ester was used in this experiment.

‖ The bromomagnesium enolate was obtained by the addition of phenylmagnesium bromide to ethyl benzylidenecyanoacetate.

§ The reactants were added in inverse order.

TABLE IX

ALKYLATION OF ALKYLIDENEMALONONITRILES AND ALKYLIDENECYANOACETIC ESTERS

Compound Alkylated	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$(C_2H_5)_2C=C(CN)_2$	CH_3I	$CH_3CH=C(C_2H_5)C(CH_3)(CN)_2$	93	$NaOC_3H_7$-i	i-C_3H_7OH	41
	C_2H_5I	$CH_3CH=C(C_2H_5)C(C_2H_5)(CN)_2$	97	$NaOC_3H_7$-i	i-C_3H_7OH	211
	$CH_2=CHCH_2Br$	$CH_3CH=C(C_2H_5)C(CH_2CH=CH_2)(CN)_2$	81	$NaOC_2H_5$	Ethanol	215
n-$C_3H_7C(CH_3)=C(CN)_2$	C_2H_5Br	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)_2$	—	$NaOC_3H_7$-i	i-C_3H_7OH	211
	C_2H_5I	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)_2$	—	$NaOC_3H_7$-i	i-C_3H_7OH	211
	$(C_2H_5)_2SO_4$	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)_2$	—	$NaOC_3H_7$-i	i-C_3H_7OH	211
⬡=$C(CN)_2$	C_2H_5I	(1-Cyclohexenyl)ethylmalononitrile	63	$NaOC_3H_7$-i	i-C_3H_7OH	211
	$CH_2=CHCH_2Br$	(1-Cyclohexenyl)allylmalononitrile	93	$NaOC_2H_5$	Ethanol	215
$C_2H_5C(CH_3)=C(CN)$-$CO_2C_2H_5$	CH_3I	$CH_2CH=C(CH_3)C(CH_3)(CN)CO_2C_2H_5$	65	$NaOC_2H_5$	Ethanol	41
	C_2H_5I	$CH_3CH=C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$	55	$NaOC_2H_5$	Ethanol	37
	n-C_3H_7I	$CH_3CH=C(CH_3)C(C_3H_7$-$n)(CN)$-$CO_2C_2H_5$	42	$NaOC_2H_5$	Ethanol	37
	$CH_2=CHCH_2Br$	$CH_3CH=C(CH_3)C(CH_2CH=CH_2)(CN)$-$CO_2C_2H_5$	34	$NaOC_2H_5$	Ethanol	214
	$CH_2=CClCH_2Cl$	Structure not determined*	Poor	$NaOC_2H_5$	Ethanol	64
	$CH_2=CBrCH_2Br$	Structure not determined*	Poor	$NaOC_2H_5$	Ethanol	64
	n-C_4H_9I	$CH_3CH=C(CH_3)C(C_4H_9$-$n)(CN)$-$CO_2C_2H_5$	40	$NaOC_2H_5$	Ethanol	37
	$CH_3CH=CHCH_2Br$	$CH_3CH=C(CH_3)$-$C(CH_2CH=CHCH_3)(CN)CO_2C_2H_5$	30	$NaOC_2H_5$	Ethanol	64
	$CH_2=C(CH_3)CH_2Cl$	$CH_3CH=C(CH_3)$-$C[CH_2C(CH_3)=CH_2](CN)CO_2C_2H_5$†	20-35	$NaOC_2H_5$	Ethanol	64
	$C_6H_5CH=CHCH_2Br$	$CH_3CH=C(CH_3)$-$C(CH_2CH=CHC_6H_5)(CN)CO_2C_2H_5$*	Poor	$NaOC_2H_5$	Ethanol	64

$n\text{-}C_3H_7C(CH_3)=C(CN)\text{-}CO_2C_2H_5$	CH_3I	$C_2H_5CH=C(CH_3)C(CH_3)(CN)CO_2C_2H_5$	68	$NaOC_2H_5$	Ethanol	37
	C_2H_5Br	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$	41	$NaOC_2H_5$	Ethanol	37
	C_2H_5I	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$	63	$NaOC_2H_5$	Ethanol	37
	C_2H_5I	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)CO_2CH_3$	17	$NaOCH_3$	CH_3OH	41
$n\text{-}C_3H_7C(CH_3)=C(CN)\text{-}CO_2CH_3$	$(C_2H_5)_2SO_4$	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)CO_2C_2H_5$	45	$NaOC_2H_5$	Ethanol	37
$n\text{-}C_3H_7C(CH_3)=C(CN)\text{-}CO_2C_2H_5$	$(C_2H_5)_2SO_4$	$C_2H_5CH=C(CH_3)C(C_2H_5)(CN)\text{-}CO_2C_3H_7\text{-}i$	73	$NaOC_3H_7\text{-}i$	$i\text{-}C_3H_7OH$	41
$n\text{-}C_3H_7C(CH_3)=C(CN)\text{-}CO_2C_3H_7\text{-}i$	$n\text{-}C_3H_7I$	$C_2H_5CH=C(CH_3)C(C_3H_7\text{-}n)(CN)\text{-}CO_2C_2H_5$	43	$NaOC_2H_5$	Ethanol	37
$n\text{-}C_3H_7C(CH_3)=C(CN)\text{-}CO_2C_2H_5$	$i\text{-}C_3H_7I$	$C_2H_5CH=C(CH_3)C(C_3H_7\text{-}i)(CN)\text{-}CO_2C_2H_5$	42	$NaOC_2H_5$	Ethanol	37
	$CH_2=CHCH_2Br$	$C_2H_5CH=C(CH_3)C(CH_2CH=CH_2)(CN)\text{-}CO_2C_2H_5$	40	$NaOC_2H_5$	Ethanol	37
$(C_2H_5)_2C=C(CN)\text{-}CO_2C_2H_5$	CH_3I	$CH_3CH=C(C_2H_5)C(CH_3)(CN)CO_2C_2H_5$	87	$NaOC_2H_5$	Ethanol	37
	C_2H_5I	$CH_3CH=C(C_2H_5)C(C_2H_5)(CN)\text{-}CO_2C_2H_5$	70	$NaOC_2H_5$	Ethanol	37
	$n\text{-}C_3H_7Br$	$CH_3CH=C(C_2H_5)C(C_3H_7\text{-}n)(CN)\text{-}CO_2C_2H_5$	57	$NaOC_2H_5$	Ethanol	37
	$i\text{-}C_3H_7I$	$CH_3CH=C(C_2H_5)C(C_3H_7\text{-}i)(CN)\text{-}CO_2C_2H_5$	63	$NaOC_2H_5$	Ethanol	37
$\triangle$ CH_2, CH_2 CHC=C(CN)-$CO_2C_2H_5$	C_2H_5I	$\triangle$ CHCC(C_2H_5)(CN)CO$_2$C$_2$H$_5$ CH_2, CH_2 =CH_2	12	$NaOC_2H_5$	Ethanol	905

Note: References 577–1080 are on pp. 322–331.

* The poor yield obtained precluded purification of product.

† The product isomerized partially on distillation.

TABLE IX—*Continued*

ALKYLATION OF ALKYLIDENEMALONONITRILES AND ALKYLIDENECYANOACETIC ESTERS

Compound Alkylated	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
$\overset{CH_2}{\underset{CH_2}{\diagup}}CHC=C(CN)-CO_2C_3H_7\text{-}i$ $\quad CH_3$	$(C_2H_5)_2SO_4$	$\diagup CHCC(C_2H_5)(CN)CO_2C_3H_7\text{-}i$ $CH_2\ \|$ CH_2	60	$NaOC_3H_7\text{-}i$	$i\text{-}C_3H_7OH$	995
$n\text{-}C_3H_7C(CH_3)=C(CN)\text{-}CO_2C_2H_5$	CH_3I	$n\text{-}C_3H_7CH=C(CH_3)C(CH_3)(CN)\text{-}CO_2C_2H_5$	78	$NaOC_2H_5$	Ethanol	37
$n\text{-}C_3H_7C(CH_3)=C(CN)\text{-}CO_2C_2H_5$	C_2H_5I	$n\text{-}C_3H_7CH=C(CH_3)C(C_2H_5)(CN)\text{-}CO_2C_2H_5$	70	$NaOC_2H_5$	Ethanol	37
$i\text{-}C_3H_9C(CH_3)=C(CN)\text{-}CO_2C_2H_5$	CH_3I	$i\text{-}C_3H_7CH=C(CH_3)C(CH_3)(CN)\text{-}CO_2C_2H_5$	79	$NaOC_2H_5$	Ethanol	41
$i\text{-}C_3H_9C(CH_3)=C(CN)\text{-}CO_2CH_3$	CH_3I	$i\text{-}C_3H_7CH=C(CH_3)C(CH_3)(CN)CO_2CH_3$	46	$NaOCH_3$	CH_3OH	37
$(CH_3)_2C=CHC(CH_3)=$ $C(CN)CO_2C_3H_7\text{-}i$	C_2H_5I CH_3I	$i\text{-}C_3H_7CH=C(CH_3)C(C_2H_5)(CN)CO_2CH_3$ $CH_2=C(CH_3)CH=C(CH_3)\text{-}$ $C(CH_3)(CN)CO_2C_3H_7\text{-}i$	32 47	$NaOCH_3$ $NaOC_3H_7\text{-}i$	CH_3OH $i\text{-}C_3H_7OH$	37 575
Ethyl cyclohexyl-idenecyanoacetate	CH_3I	Ethyl methyl-(1-cyclohexenyl)-cyanoacetate	—	$NaOC_2H_5$	Ethanol	996, 997
	C_2H_5I	Ethyl ethyl-(1-cyclohexenyl)-cyanoacetate	45	$NaOC_2H_5$	Ethanol	259
	$CH_2=CHCH_2Br$	Ethyl allyl-(1-cyclohexenyl)-cyanoacetate	79	$NaOC_2H_5$	Ethanol	215
	$n\text{-}C_4H_9I$	Ethyl n-butyl-(1-cyclohexenyl)-cyanoacetate	60	$NaOC_2H_5$	Ethanol	259
	2-Methyl-2-cyclo-pentenyl bromide	Ethyl (2-methyl-2-cyclo-pentenyl)-(1-cyclohexenyl)-cyanoacetate	52	$NaOC_3H_7\text{-}i$	$i\text{-}C_3H_7OH$	247

$n\text{-}C_5H_{13}CH{=}C(CN)\cdot CO_2C_2H_5$	$n\text{-}C_4H_9I$	$n\text{-}C_5H_{11}CH{=}CHC(C_4H_9\text{-}n)(CN)\cdot CO_2C_2H_5$	10	$NaOC_2H_5$	Ethanol	259
$n\text{-}C_5H_{11}C(CH_3){=}C(CN)\cdot CO_2CH_3$	CH_3I	$n\text{-}C_4H_9CH{=}C(CH_3)C(CH_3)(CN)\cdot CO_2CH_3$	23	$NaOCH_3$	CH_3OH	37
$n\text{-}C_4H_9CH{=}C(CH_3)C(CN)\cdot CO_2C_2H_5$	CH_3I	$n\text{-}C_4H_9CH{=}C(CH_3)C(CH_3)(CN)\cdot CO_2C_2H_5$	62	$NaOC_2H_5$	Ethanol	41
$n\text{-}C_4H_9CH{=}C(CH_3)C(CN)\cdot CO_2CH_3$	C_2H_5I	$n\text{-}C_4H_9CH{=}C(CH_3)C(C_2H_5)(CN)\cdot CO_2CH_3$	18	$NaOCH_3$	CH_3OH	37
$n\text{-}C_4H_9CH{=}C(CH_3)C(CN)\cdot CO_2CH_3$	$(C_2H_5)_2SO_4$	$n\text{-}C_4H_9CH{=}C(CH_3)C(C_2H_5)(CN)\cdot CO_2CH_3$	13	$NaNH_2$	Toluene	37
$n\text{-}C_5H_{11}C(CH_3){=}C(CN)\cdot CO_2C_2H_5$	$CH_2{=}C(CH_3)CH_2Cl$	$n\text{-}C_5H_{11}C(CH_3){=}C(CH_3)\cdot C[CH_2C(CH_3){=}CH_2](CN)CO_2C_2H_5$†	20–35	$NaOC_2H_5$	Ethanol	64
$(n\text{-}C_3H_7)_2C{=}C(CN)\cdot CO_2C_2H_5$	CH_3I	$C_2H_5CH{=}C(C_3H_7\text{-}n)C(CH_3)(CN)\cdot CO_2C_2H_5$	81	$NaOC_2H_5$	Ethanol	41
$(n\text{-}C_3H_7)_2C{=}C(CN)\cdot CO_2CH_3$	C_2H_5I	$C_2H_5CH{=}C(C_3H_7\text{-}n)C(C_2H_5)(CN)\cdot CO_2CH_3$	78	$NaOCH_3$	CH_3OH	37
$(n\text{-}C_3H_7)_2C{=}C(CN)\cdot CO_2CH_3$	$(C_2H_5)_2SO_4$	$C_2H_5CH{=}C(C_3H_7\text{-}n)C(C_2H_5)(CN)\cdot CO_2CH_3$	58	Na	Ether	37
Ethyl 2-methylcyclohexylidenecyanoacetate	CH_3I	Ethyl methyl-(2-methyl-1-cyclohexenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	353
Ethyl 3-methylcyclohexylidenecyanoacetate	CH_3I	Ethyl methyl-(3-methyl-1-cyclohexenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	353
Ethyl 4-methylcyclohexylidenecyanoacetate	CH_3I	Ethyl methyl-(4-methyl-1-cyclohexenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	353
	$C_6H_5COCH_2Br$	Ethyl phenacyl-(4-methyl-1-cyclohexenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	997
$C_6H_5CH_2C(CH_3){=}C(CN)\cdot CO_2C_2H_5$	C_2H_5X‡	$C_6H_5CH{=}C(CH_3)C(C_2H_5)(CN)\cdot CO_2C_2H_5$	—	Na	C_6H_6	74
$C_6H_5C(C_2H_5){=}C(CN)\cdot CO_2C_2H_5$	C_2H_5X‡	$CH_3CH{=}C(C_6H_5)C(C_2H_5)(CN)\cdot CO_2C_2H_5$	—	Na	C_6H_6	74

Note: References 577–1080 are on pp. 322–331.

† The product isomerized partially on distillation.

‡ The halogen was not specified.

TABLE IX—*Continued*

ALKYLATION OF ALKYLIDENEMALONONITRILES AND ALKYLIDENECYANOACETIC ESTERS

Compound Alkylated	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
Ethyl 1-indanylidene-cyanoacetate	CH_3I	Ethyl methyl-(3-indenyl)cyanoacetate	70	$NaOC_2H_5$	Ethanol	181
	C_2H_5I	Ethyl ethyl-(3-indenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	181
	$n\text{-}C_3H_7I$	Ethyl n-propyl-(3-indenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	181
	$i\text{-}C_3H_7I$	Ethyl isopropyl-(3-indenyl)cyano-acetate	60	$NaOC_2H_5$	Ethanol	181
			36	$NaOC_2H_5$	Ethanol	217
	$CH_2{=}CHCH_2Br$	Ethyl allyl-(3-indenyl)cyanoacetate	65	$NaOC_2H_5$	Ethanol	181
	$CH_2{=}CHCH_2I$	Ethyl allyl-(3-indenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	181
	$i\text{-}C_4H_9I$	Ethyl i-butyl-(3-indenyl)cyanoacetate	—	$NaOC_2H_5$	Ethanol	181
	$i\text{-}C_5H_{11}I$	Ethyl i-amyl-(3-indenyl)cyanoacetate	70	$NaOC_2H_5$	Ethanol	181
Ethyl 2-indanyl-idenecyanoacetate§	CH_3I	Ethyl methyl-(2-indenyl)cyanoacetate				
C(CN)CO₂C₂H₅ structure	$ClCH_2CO_2C_2H_5$	CH₂CO₂C₂H₅ / NCCCO₂C₂H₅ structure	55	$NaOCH_3$	C_6H_6	998

§ This ester may be ethyl 2-indenylcyanoacetate as designated in ref. 181.

TABLE X

ALKYLATION OF MALONONITRILE AND MONOALKYLMALONONITRILES, $RCH(CN)_2$

R	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
H	C_1					
	CH_3I	$(CH_3)_2C(CN)_2$	Poor	Dry silver salt	None	104
	CH_3I	$\{[(CH_3)_2C(CN)_2$	ca. 14	$NaOCH_3$	CH_3OH	104
		$\{(CH_3)_2C(CN)C(=NH)OCH_3$	55			
	CH_3I	$(CH_3)_2C(CN)_2$	36	$NaOC_2H_5$	None	104, 999
	$CHCl_3$	$(NC)_2CHCH=C(CN)C(=NH)OC_2H_5$	—	$NaOC_2H_5$	Ethanol	231
	C_2					
	C_2H_5I	$(C_2H_5)_2C(CN)_2$	32	$NaOC_2H_5$	None	104, 999
	C_2H_5I	$\{[(C_2H_5)_2C(CN)C(=NH)OC_2H_5$	Good	$NaOC_2H_5$	Ethanol	104
		$\{(C_2H_5)_2C(CN)_2$	—			
	C_3-C_9					
	$n\text{-}C_3H_7Cl$	$(n\text{-}C_3H_7)_2C(CN)_2$	—	$NaOC_2H_5$	Ethanol	999
	$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2C(CN)_2$	—	Na	Ether	95
	$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2C(CN)_2$	32	$NaOC_2H_5$	Ethanol	95, 999
	2,3-Dibromoindone	Bromoindonylmalononitrile*	100	$NaOC_2H_5$	Ethanol	781
C_2H_5	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_2H_5)(CN)C(=NH)OC_2H_5$	71	$NaOC_2H_5$	Ethanol	95
C_6H_5	CH_3I	$C_6H_5C(CH_3)(CN)C(=NH)OC_2H_5$	ca. 100	$NaOC_2H_5$	Ethanol	333
	$Cl(CH_2)_3Br$	$Cl(CH_2)_3C(C_6H_5)(CN)_2$	40	$NaOC_2H_5$	Ethanol	1000
	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_6H_5)(CN)_2$	100	$NaOC_2H_5$	Ethanol	333
$C_6H_5CH_2$	CH_3I	$C_6H_5CH_2C(CH_3)(CN)_2$	—	Dry sodium salt	None	333
	CH_3I	$C_6H_5CH_2C(CH_3)(CN)_2$	92	Dry silver salt	Ether	95
	CH_3I	$C_6H_5CH_2C(CH_3)(CN)C(=NH)OC_2H_5$	85	$NaOC_2H_5$	Ethanol	95
	C_2H_5I	$C_6H_5CH_2C(C_2H_5)(CN)C(=NH)OC_2H_5$	75	$NaOC_2H_5$	Ethanol	95

Note: References 577–1080 are on pp. 322–331.

* The structure of this product was not determined.

TABLE XI

ALKYLATION OF MONOCARBOXYLIC ESTERS, $RCH(R')CO_2R''$

(The ethyl ester was used unless otherwise indicated.)

R'	R''	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
H	H	C_2H_5Br	$n\text{-}C_3H_7CO_2C_2H_5$	5	K	Ether	190
H		$C_6H_5CH_2Cl$	$C_6H_5(CH_2)_2CO_2C_2H_5$	Poor	$NaC(C_6H_5)_3$	Ether	08
H		C_2H_5I	$i\text{-}C_3H_7CH(C_2H_5)CO_2C_2H_5$	22	$NaC(C_6H_5)_3$	Ether	08
H		C_2H_5I	$i\text{-}C_3H_7CH(C_2H_5)CO_2C_2H_5$	33	$NaC(C_6H_5)_3$	Ether	09
H	C_6H_5	$C_2H_5SO_3C_3H_5$	$C_6H_5CH(C_2H_5)CO_2C_2H_5$	35	K	Ether	190
H		C_2H_5Br	$C_6H_5CH(C_2H_5)CO_2C_2H_5$	—	Na	Ether	240
		$CH_3N(CH_2CH_2Cl)_2$	Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate	—	$NaOC_2H_5$	Ethanol	504
		$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2CH(C_6H_5)CO_2C_2H_5$	17	KOH	$CH_3CH(OC_2H_5)_2$	81
		$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CO_2C_2H_5$	38	KOH	1-Butoxy-2-ethoxyethane	81
		$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CO_2C_2H_5$	30 (50)	KOH	$CH_3CH(OC_3H_7\text{-}n)_2$	83, 81; 1001
		$C_6H_5CH_2Cl$	None	—	$NaOC_2H_5$	Ethanol	178
		4,7-Dichloroquinoline	Ethyl α-phenyl-α-(7-chloro-4-quinolyl)acetate / α-Phenyl-α-(7-chloro-4-quinolyl)acetamide	1	$NaNH_2$	C_6H_6	
CH_3	CH_3	I_2	$C_2H_5O_2CC(CH_3)_2C(CH_3)_2CO_2C_2H_5$	20	$NaC(C_6H_5)_3$	Ether	09
		CH_3I	$(CH_3)_3CCO_2C_2H_5$	28	$NaC(C_6H_5)_3$	Ether	08
		C_2H_5I	$C_2H_5C(CH_3)_2CO_2C_2H_5$	55	$NaC(C_6H_5)_3$	Ether	08
		$\underset{O}{\underset{\diagdown\diagup}{CH_2\text{—}CH_2}}$	$\begin{array}{c}CH_2CH_2C(CH_3)_2\\ \,\,\,\mid \qquad\qquad\mid\\ O\!\!-\!\!-\!\!-\!\!-\!\!CO\end{array}$	58	$NaC(C_6H_5)_3$	Ether	09
		$(CH_3)_2CBrCO_2C_2H_5$	$C_2H_5O_2CC(CH_3)_2C(CH_3)_2CO_2C_2H_5$	55	$NaC(C_6H_5)_3$	Ether	69
		$C_6H_5CH_2Cl$	$C_6H_5CH_2C(CH_3)_2CO_2C_2H_5$	30	KOH	$CH_3CH(OC_2H_5)_2$	81
		$C_6H_5CH_2Cl$	$C_6H_5CH_2C(CH_3)_2CO_2C_2H_5$	23	KOH	1-Butoxy-2-ethoxyethane	81
CH_3		$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_2H_5)CO_2C_2H_5$	24	$NaC(C_6H_5)_3$	Ether	08
C_2H_5		$n\text{-}C_3H_7I$	$n\text{-}C_3H_7CH(C_2H_5)CO_2C_2H_5$	42	$NaC(C_6H_5)_3$	Ether	08

Halide	Product	Condensing agent	Yield (%)	Solvent	Reference
(continued from previous page)		NaNH₂	57	Toluene	1002
β-(4-Morpholinyl)-ethyl chloride	Ethyl α-α-dl-(2-thienyl)-γ-(4-morpholinyl)butyrate	NaC(C₆H₆)₃	—	Ether	07
I₂	CH₃O₂CC(CH₃)₂C(C₆H₅)₂CO₂CH₃*	KNH₂	—	Liquid NH₃	1003
CH₃I	(C₆H₅)₂C(CH₃)CO₂C₂H₅	NaNH₂	Good	Ether	62
CH₃X†	(C₆H₅)₂C(CH₃)CO₂CH₂C₆H₅‡	NaOC₂H₅	81	None	180
C₂H₅I	(C₂H₅)₂C(C₂H₅)CO₂C₂H₅	KOC₂H₅	100	C₆H₆-ether	1003
C₂H₅I	(C₆H₅)₂C(C₂H₅)CO₂C₂H₅	NaNH₂	30	Ether	62
i-C₃H₇X†	(C₆H₅)₂C(C₃H₇-i)CO₂CH₂C₆H₅‡	NaNH₂	77	C₆H₆	1004
CH₂=CHCH₂X†	CH₂=CHCH₂C(C₆H₅)₂CO₂H§	NaNH₂	100	Ether	62
CH₂=CHCH₂X†	CH₂=CHCH₂C(C₆H₅)₂CO₂CH₂C₆H₅‡	[(C₂H₅)₂CCN]Na	—	C₆H₆-C₆H₅Cl	93
β-(4-Morpholinyl)-ethyl chloride	Ethyl α,α-diphenyl-γ-(4-morpholinyl)butyrate	NaOC₂H₅	—	Ethanol	564
C₆H₅CH₂Cl	None*	NaC(C₆H₆)₃	—	C₆H₆	07
C₆H₅CH₂Cl	C₆H₅CH₂C(C₆H₅)₂CO₂CH₃*	NaNH₂	—	Ether	61,1005
C₆H₅CH₂Cl	C₆H₅CH₂C(C₆H₅)₂CO₂CH₂C₆H₅‡	[(C₂H₅)₂CCN]Na	—	C₆H₆-C₆H₅Cl	93
β-(2-Methyl-1-pyrrolidyl)ethyl chloride	Ethyl α,α-diphenyl-γ-(2-methyl-1-pyrrolidyl)butyrate	[(C₂H₅)₂CCN]Na	90	C₆H₆	01,93
β-(1-Piperidyl)ethyl chloride	Ethyl α,α-diphenyl-γ-(1-piperidyl)butyrate	[(C₂H₅)₂CCN]Na	—	C₆H₆	91
β-(4-Morpholinyl)-propyl chloride	Ethyl α,α-diphenyl-γ-(4-morpholinyl)valerate	[(C₂H₅)₂CCN]Na	—	C₆H₆	91
γ-(1-Piperidyl)-propyl chloride	Ethyl α,α-diphenyl-δ-(1-piperidyl)valerate	[(C₂H₅)₂CCN]Na	—	C₆H₆	91
β-(1-Piperidyl)-propyl chloride	Ethyl α,α-diphenyl-γ-(1-piperidyl)valerate	[(C₂H₅)₂CCN]Na	—	C₆H₆	91
C₆H₅CHBrCO₂CH₃	CH₃O₂CCH(C₆H₅)CH(C₆H₅)CO₂CH₃*	(C₆H₅)₃CNa	Poor	Ether	07
β-(2-Methyl-5-ethyl-1-piperidyl)propyl chloride	Ethyl α,α-diphenyl-γ-(2-methyl-5-ethyl-1-piperidyl)valerate	[(C₂H₅)₂CCN]Na	—	C₆H₆	91
(C₂H₅)₂CHBr	(C₆H₅)₂CHC(C₂H₅)₂CO₂CH₃*	NaC(C₆H₃)₃	—	Toluene	07
(C₂H₅)₃CCl	(C₆H₅)₃CC(C₂H₅)₂CO₂CH₃*	NaC(C₆H₅)₃	—	Ether	07

(Structure at lower left, with ring labels: S, C₆H₅, C₆H₅)

Note: References 557–1030 are on pp. 322–331.

* The methyl ester was used in this experiment.

† The halogen was not specified.

‡ The benzyl ester was used in this experiment.

§ The allyl ester was used in this experiment.

TABLE XI—*Continued*

ALKYLATION OF MONOCARBOXYLIC ESTERS, $RCH(R')CO_2R''$

(The ethyl ester was used unless otherwise indicated.)

R	R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
o,o'-Diphenylene		I_2	Diethyl 2,3-bis-(o,o'-diphenylene)succinate	—	$NaOC_2H_5$	Ethanol-ether	248
		I_2	Diethyl 2,3-bis-(o,o'-diphenylene)succinate	—	KOC_2H_5	Ethanol-ether	248
		CH_3I	Ethyl 9-methylfluorene-9-carboxylate	Good	KOC_2H_5	Ether	248
		C_2H_5I	Ethyl 9-ethylfluorene-9-carboxylate	Good	KOC_2H_5	Ether	248
		$Br(CH_2)_2Br$	Diethyl α,α'-bis-(o,o'-diphenylene)adipate	—	KOC_2H_5	Ethanol	248
		$CH_2{=}CHCH_2Br$	Ethyl 9-allylfluorene-9-carboxylate	—	KOC_2H_5	Ether	248
		$ClCH_2CO_2C_2H_5$	Diethyl α-(o,o'-diphenylene)succinate	—	KOC_2H_5	Ether	248
		$I(CH_2)_2CO_2C_2H_5$	Diethyl α-(o,o'-diphenylene)glutarate	—	KOC_2H_5	Ether	248
		C_2H_5I	None	—	KOC_2H_5	Ether	248
		2,4-Dinitrobromobenzene	Ethyl 9-(2',4'-dinitrophenyl)fluorene-9-carboxylate	40	$[(C_2H_5)_2CCN]Na$	C_6H_6-C_6H_5Cl	91, 93
		β-(4-Morpholinyl)ethyl chloride	Ethyl 9-[β-(4-morpholinyl)ethyl]fluorene-9-carboxylate	85	KOC_2H_5	Ether	248
		$C_6H_5CH_2Cl$	Ethyl 9-benzylfluorene-9-carboxylate	—	KOC_2H_5	Ethanol-ether	93
		β-(1-Piperidyl)ethyl chloride	Ethyl 9-[β-(1-piperidyl)ethyl]fluorene-9-carboxylate	—	KOC_2H_5	Ether	248
		$C_6H_5COCH_2Br$	Ethyl 9-phenacylfluorene-9-carboxylate	—	$NaNH_2$	Ether	60
C_6H_5	p-Tolyl	CH_3I	$p\text{-}CH_3C_6H_4C(CH_3)(C_6H_5)CO_2CH_2C_6H_5$‡	—	$NaNH_2$	Ether	60
		$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_6H_5)(C_6H_4CH_3\text{-}p)CO_2CH_2C_6H_5$‡	65	$NaNH_2$	Ether	60
		$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_6H_5)(C_6H_4CH_3\text{-}p)CO_2CH_2C_6H_5$‡	—	$NaNH_2$	Ether	60
$n\text{-}C_7H_{15}$	$n\text{-}C_7H_{15}$	CH_3I	$(n\text{-}C_7H_{15})_2C(CH_3)CO_2CH_3$*	77	$NaC(C_6H_5)_3$	Ether	70
C_6H_5	Veratryl	β-(4-Morpholinyl)ethyl chloride	Ethyl α-phenyl-α-veratryl-γ-(4-morpholinyl)butyrate	48	$[(C_2H_5)_2CCN]Na$	C_6H_6-C_6H_5Cl	93

			64	NaC(C$_6$H$_5$)$_3$	Ether	1006
			7			
n-C$_{14}$H$_{29}$C(CH$_3$)(C$_7$H$_{15}$-n)CO$_2$CH$_3$*	CH$_3$I		—	NaC(C$_6$H$_5$)$_3$	Ether	70
n-C$_{12}$H$_{25}$C(CH$_3$)(C$_{10}$H$_{21}$-n)CO$_2$CH$_3$*	CH$_3$I		73	NaC(C$_6$H$_5$)$_3$	Ether	70
n-C$_{12}$H$_{25}$C(C$_2$H$_5$)(C$_{10}$H$_{21}$-n)CO$_2$CH$_3$*	C$_2$H$_5$I		40	NaC(C$_6$H$_5$)$_3$	Ether	70

n-C$_7$H$_{15}$ n-C$_{14}$H$_{29}$
n-C$_{10}$H$_{21}$ n-C$_{12}$H$_{25}$

Note: References 577–1030 are on pp. 322–331.
* The methyl ester was used in this experiment.
‡ The benzyl ester was used in this experiment.

TABLE XII

ALKYLATION OF 3-ARYL-2-BENZOFURANONES TO
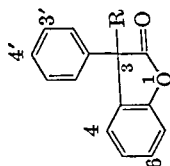
Substituents	Alkylating Agent	R in Product	Yield, %	Base	Solvent	Reference
None	I$_2$	C$_6$H$_5$	—	NaOC$_2$H$_5$	Ether	262
	CH$_3$I	—CH$_3$	ca. 100	KOC$_2$H$_5$	Ethanol	262
	C$_2$H$_5$I	—C$_2$H$_5$	85	—	—	262
	CH$_2$=CHCH$_2$Br	—CH$_2$CH=CH$_2$	80	KOC$_2$H$_5$	Ether	574
	Br(CH$_2$)$_3$Cl	—(CH$_2$)$_3$Cl	42	NaH	C$_6$H$_6$	574, 1007, 1008
	Br(CH$_2$)$_3$CN	—(CH$_2$)$_3$CN	68	NaH	C$_6$H$_6$	574
	(CH$_3$)$_2$N(CH$_2$)$_2$Cl	—(CH$_2$)$_2$N(CH$_3$)$_2$	24	Na	Toluene	574
	n-C$_4$H$_9$NH(CH$_2$)$_2$Cl	—(CH$_2$)$_2$NHC$_4$H$_9$-n	—	Na	Toluene	574
	(C$_2$H$_5$)$_2$N(CH$_2$)$_2$Cl	—(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	87	Na	Toluene	574, 1007, 1008
	β-(4-Morpholinyl)ethyl chloride	β-(4-Morpholinyl)ethyl	66	NaH	C$_6$H$_6$	574, 1007, 1008
	(C$_2$H$_5$)$_2$N(CH$_2$)$_3$Br	—(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	16	Na	Toluene	574

$(C_2H_5)_2NCH_2CH(CH_3)Cl$	$-CH(CH_3)CH_2N(C_2H_5)_2$	80	NaH	Toluene	1007, 1008
$(C_2H_5)_2NCH(CH_3)CH_2Cl$	$-CH_2CH(CH_3)N(C_2H_5)_2$	81	NaH	Toluene	574, 1007, 1008
$C_6H_5CH_2Br$	$-CH_2C_6H_5$	ca. 100	—	—	262
β-(1-Piperidyl)ethyl chloride	β-(1-Piperidyl)ethyl	78	Na	Toluene	574
γ-(4-Morpholinyl)propyl chloride	γ-(4-Morpholinyl)propyl	64	NaH	C_6H_6	574, 1007, 1008
$(C_2H_5)_2N(CH_2)_2Cl$	$-(CH_2)_2N(C_2H_5)_2$	17	Na	Toluene	574
$NCH_2C(CH_3)_2CH_2Cl$	$-CH_2C(CH_3)_2CH_2N$	73	NaH	C_6H_6	574, 1007, 1008
$(n\text{-}C_4H_9)_2N(CH_2)_2Cl$	$-(CH_2)_2N(C_4H_9\text{-}n)_2$	74	Na	Toluene	574
$(n\text{-}C_4H_9)_2N(CH_2)_3Cl$	$-(CH_2)_3N(C_4H_9\text{-}n)_2$	33	Na	Toluene	574
$C_6H_5CH_2N(C_4H_9\text{-}n)(CH_2)_2Cl$	$-(CH_2)_2N(C_4H_9\text{-}n)CH_2C_6H_5$	63	NaH	C_6H_6	1007, 574, 1008
$(C_2H_5)_2N(CH_2)_{11}Cl$	$-(CH_2)_{11}N(C_2H_5)_2$	—	—	—	1007, 1008
		42	Na	Ether	263
5-Cl $(C_2H_5)_2N(CH_2)_2Cl$	$-(CH_2)_2N(C_2H_5)_2$	70	Na	Toluene	574, 1007, 1008
5-Br $(C_2H_5)_2N(CH_2)_2Cl$	$-(CH_2)_2N(C_2H_5)_2$	71	Na	Toluene	574, 1007, 1008

Note: References 577-1080 are on pp. 322-331.

TABLE XIV

ALKYLATION OF MONONITRILES, RCH(R')CN

R' = H   R = H

Alkylating Agent	Product	Yield %	Base	Solvent	Reference
C_2					
C_2H_5Cl	$(C_2H_5)_3CCN$	—	$NaNH_2$	Paraffin oil	122, 1013
C_2H_5Cl	$C_2H_5CH_2CN$	58	$NaNH_2$	Liquid NH_3	323
C_2H_5Br	$(C_2H_5)_2CHCN$	20	$NaNH_2$	Ether	53
C_2H_5Br	$(C_2H_5)_2CHCN$	ca. 70	$NaNH_2$	Ether	1014
C_2H_5Br	$n\text{-}C_3H_7CN$	23			
C_2H_5Br	$(C_2H_5)_2CHCN$	24			
C_2H_5Br	$(C_2H_5)_3CCN$	15			
C_3–C_5					
$CH_2{=}CHCH_2Cl$	$(CH_2{=}CHCH_2)_2CCN$	87	$NaNH_2$	Ether	122, 1013
$CH_2{=}CHCH_2Cl$	$(CH_2{=}CHCH_2)_3CCN$	80–90	$NaNH_2$	C_2H_6	53, 122
$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2CH_2CN$	—	$NaNH_2$	CH_3CN	1013
$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2CH_2CN$	—	$NaNH_2$	CH_3CN	1013
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9CH_2CN$	56	$NaNH_2$	Liquid NH_3	323
$n\text{-}C_4H_9Br$	$(n\text{-}C_4H_9)_2CHCN$	27	$NaNH_2$	Ether	53, 122, 1013
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9CH_2CN$	60	$NaNH_2$	Ether	
$n\text{-}C_4H_9Br$	$(n\text{-}C_4H_9)_2CHCN$	0	$NaNH_2$	Toluene	1015
$n\text{-}C_4H_9Br$	$(n\text{-}C_4H_9)_2CCN$	80	$NaNH_2$	Liquid NH_3	323
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9CH_2CN$	63	$NaNH_2$	Toluene	1015
$n\text{-}C_4H_9OSO_2C_6H_4CH_3\text{-}?$	$(n\text{-}C_4H_9)_2CHCN$	20	$NaNH_2$	Toluene	1016
$n\text{-}C_5H_{11}Br$	$n\text{-}C_5H_{11})_3CCN$	57	$NaNH_2$		
2-Bromopyridine	Di-(2-pyridyl)acetonitrile	25		Liquid NH_3	323
C_6–C_7					
C_6H_5Cl	$C_6H_5CH_2CN$	31	KNH_2	Liquid NH_3	1017
C_6H_5Cl	$(C_6H_5)_2CHCN$	28			1017
$C_6H_5CH_2Cl$	None	—	Na	C_6H_6	
$C_6H_5CH_2Cl$	None	—	$NaOC_2H_5$	Ethanol	323
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH_2CN$	15–38	$NaNH_2$	Liquid NH_3	
$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2CHCN$	10–40			
$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2CCN$	2		C_6H_6	53
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH_2CN$	40	$NaNH_2$	Liquid NH_3	

R	R'	Halide	Nitrile	Yield (%)	Condensing Agent	Solvent	Reference
	C_2–C_{10}						
H	CH_3	C_2H_5I	$C_2H_5CH(CH_3)CN$	—	Na	Ether	71
		C_2H_5I	None	—	Na	C_6H_6	71
		C_2H_5Cl	$C_6H_5CH(CH_3)CN$	43	KNH_2	Liquid NH_3	323
		$n\text{-}C_7H_{15}Br$	$(n\text{-}C_7H_{15})_2C(CH_3)CN$	43	$NaNH_2$	Toluene	1015
		$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(CH_3)CN$	90	$NaNH_2$	Dioxane	122
		$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(CH_3)CN$	55	$NaNH_2$	C_6H_6	53
		$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2C(CH_3)CN$	100	$NaNH_2$	C_6H_6	53
		$C_6H_5CH_2X$•	$(C_6H_5CH_2)_2C(CH_3)CN$	—	$NaNH_2$	Ether	1018
		$n\text{-}C_{10}H_{21}Br$	$n\text{-}C_{10}H_{21}CH(CH_3)CN$	—	$NaNH_2$	Toluene	289
	C_2–C_8						
H	C_2H_5	C_2H_5Br	$(C_2H_5)_2CHCN$	77	$NaNH_2$	Ether	53, 122, 1013
			$(C_2H_5)_3CCN$	3	$NaNH_2$		53
		$n\text{-}C_3H_7Br$	$n\text{-}C_3H_7CH(C_2H_5)CN$	65	$NaNH_2$	Ether	53
			$(n\text{-}C_3H_7)_2C(C_2H_5)CN$	13	$NaNH_2$		53, 122
		$i\text{-}C_3H_7Br$	$i\text{-}C_3H_7CH(C_2H_5)CN$	71	$NaNH_2$	Ether	53, 122
		$CH_2=CHCH_2Cl$	$(CH_2=CHCH_2)_2C(C_2H_5)CN$	83	$NaNH_2$	C_6H_6	53
		$n\text{-}C_4H_9Cl$	$n\text{-}C_4H_9CH(C_2H_5)CN$	68	$NaNH_2$	$n\text{-}C_4H_9Cl$	122
		$C_2H_5O(CH_2)_2Cl$	$C_6H_5O(CH_2)_2CH(C_2H_5)CN$	—	$NaNH_2$	Ether	53
		$C_6H_5O(CH_2)_2Br$	$C_6H_5O(CH_2)_2CH(C_2H_5)CN$	—	$NaNH_2$	C_6H_6	75, 78
H	$ClCH_2CH_2$	None	Cyclopropanecarbonitrile	42	NaOH	None	470, 478, 1019, 1020, 1021
		None	Cyclopropanecarbonitrile	—	KOH	None	
		None	Cyclopropanecarbonitrile	80–90	$NaNH_2$	Liquid NH_3	
H	$CH_2=CH$	$CH_2=CHCH_2Br$	$(CH_2=CHCH_2)_2C(CH=CH_2)CN$	31	$NaNH_2$	Liquid NH_3	171
H	$n\text{-}C_3H_7$	$(C_2H_5)_2SO_4$	$n\text{-}C_3H_7CH(C_2H_5)CN$	—	$NaNH_2$	Inert solvent	249
		$n\text{-}C_3H_7Br$	$(n\text{-}C_3H_7)_2CCN$	76	$NaNH_2$	Toluene	1015
H	$ClCH_2CH(CH_3)$	None	2-Methylcyclopropane-carbonitrile	57	$NaNH_2$	Liquid NH_3–ether	1022
H	$CH_2=CHCH_2$	C_2H_5Br	$CH_2=CHCH_2C(C_2H_5)_2CN$	Excellent	$NaNH_2$	C_6H_6	122
H	$n\text{-}C_4H_9$	$n\text{-}C_4H_9Br$	$(n\text{-}C_4H_9)_2CHCN$	—	$NaNH_2$	Toluene	1015
			$(n\text{-}C_4H_9)_2CCN$	81	$NaNH_2$	Toluene	
		$n\text{-}C_6H_{13}Br$	$(n\text{-}C_7H_{15})_2C(C_4H_9\text{-}n)CN$	62	$NaNH_2$	Toluene	1015

Note: References 577–1080 are on pp. 322–331.

• The halogen was not specified.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield %	Base	Solvent	Reference
H	n-C4H9 (Cont.)	C6H5CH2Cl	C6H5CH2CH(C4H9-n)CN	—	NaNH2	Ether	50
H		n-C8H17Br	(n-C8H17)2C(C4H9-n)CN	70	NaNH2	C6H6	53, 1013
H	[2-thienyl] (=C4H3S)	(CH3)2N(CH2)2Cl	(CH3)2N(CH2)2CH(C4H3S)CN	42	NaNH2	C6H6	254
		2-Cyclopentenyl chloride	2-Thienyl-(2-cyclopentenyl)acetonitrile	60	NaNH2	Toluene	187
		Cyclohexyl bromide	Cyclohexyl-(2-thienyl)acetonitrile	48	NaNH2	Toluene	1023
		2-Cyclohexenyl bromide	2-Thienyl-(2-cyclohexenyl)acetonitrile	54	KOH	CH3CH(OC4H9-n)2	187
		2-Cyclohexenyl bromide	2-Thienyl-(2-cyclohexenyl)acetonitrile	42	NaOCH3	Dioxane	187
		2-Cyclohexenyl bromide	None	—	LiNH2	Toluene	187
		2-Cyclohexenyl bromide	2-Thienyl-(2-cyclohexenyl)acetonitrile	50	NaNH2	Toluene	187
H	CH3CH=C(C2H5)	CH2=CHCH2Br	CH3CH=C(C2H5)CH(CH2CH=CH2)CN	38	NaNH2	Ether	171
H	(C2H5)2NCH2	n-C4H9Br	(C2H5)2NCH2CH(C4H9-n)CN	10	NaNH2	Toluene	1015
			(C2H5)2NCH2C(C4H9-n)2CN	72	NaNH2	Toluene	
H	[5-methyl-2-thienyl]	(CH3)2NCH2Cl	(CH3)2NCH2CH(C5H5S)CN	31	NaNH2	Toluene	254
H	[2-methylpyridyl]	(CH3)2N(CH2)2Cl	(CH3)2N(CH2)2CH(C5H4N)CN	48	NaNH2	Toluene	254
H	[pyridyl]	(CH3)2N(CH2)2Cl	(CH3)2N(CH2)2CH(C5H4N)CN	40	NaNH2	C6H6	254
H	n-C6H13	C6H5CH2Cl	C6H5CH2CH(C6H13-n)CN	—	NaNH2	Ether	50
H	cyclo-C6H11	(CH3)2N(CH2)2Cl	(CH3)2N(CH2)2CH(C6H11)CN	50	NaNH2	C6H6	254

R	R′	Alkylating agent	Product	Yield (%)	Reagent	Solvent	Reference
H	1-Cyclohexenyl (=C₆H₉)	CH₂=CHCH₂Br	$CH_2=CHCH_2CH(C_6H_9)CN$	10	NaNH₂	Liquid NH₃-ether	171
			$(CH_2=CHCH_2)_2C(C_6H_9)CN$	40			
H	C₆H₅	**C₁**					
		CH₃I	$C_6H_5CH(CH_3)CN$	—	NaOC₂H₅	Ethanol	256,1024
		CH₃I	$C_6H_5CH(CH_3)CN$	—	Na	Liquid NH₃	1025
		CH₃I	$C_6H_5CH(CH_3)CN$	68–72	NaNH₂	None	1026,806
		CH₃I	$C_6H_5CH(CH_3)CN$	66	NaNH₂	Ether	583
		CH₃I	$C_6H_5C(OH)_2CN$	62	NaNH₂	Ether	1027, 1028
		CH₃I	$C_6H_5CH(CH_3)CN$	50	NaNH₂	Liquid NH₃-ether	105
			$C_6H_5C(CH_3)_2CN$	19			
		(CH₃)₂SO₄	$C_6H_5CH(CH_3)CN$	67	NaNH₂	Ether	359,992
		CH₂I₂	$C_6H_5CH(CN)CH_2CH(C_6H_5)CN$	31	NaOH	None	76
		CHCl₃	$C_6H_5CH(CN)CH=C(C_6H_5)-C(=NH)OC_2H_5$	—	NaOC₂H₅	Ethanol	231
		C₂					
		C₂H₅Cl	$C_6H_5CH(C_2H_5)CN$	Good	$[C_6H_5CH_2N(C_2H_5)_3]OH$	H₂O	84
		C₂H₅Br	$C_6H_5CH(C_2H_5)CN$	Poor	$[C_6H_5CH_2N(C_2H_5)_3]OH$	H₂O	84
		C₂H₅Br	$C_6H_5CH(C_2H_5)CN$	—	Na	Liquid NH₃	1025
		C₂H₅Br	$C_6H_5CH(C_2H_5)CN$	—	NaNH₂	Liquid NH₃	1029
		C₂H₅Br	$C_6H_5CH(C_2H_5)CN$	87	NaNH₂	Ether	1030, 1031
		C₂H₅Br	$C_6H_5CH(C_2H_5)CN$	86	NaNH₂	C₆H₆	1032
		C₂H₅I	None	—	$[C_2H_5CH_2N(C_2H_5)_3]OH$	H₂O	84
		C₂H₅I	$C_6H_5CH(C_2H_5)CN$	Poor	NaOC₂H₅	Ethanol	564
		C₂H₅I	$C_6H_5CH(C_2H_5)CN$	—	NaNH₂	None	1033
		C₂H₅I	$C_6H_5OH(C_2H_5)CN$	70–80	NaNH₂	Ether	1034
		C₂H₅I	$C_6H_5C(C_2H_5)_2CN$	—	NaNH₂	Ether	1035
		C₂H₅I	$C_6H_5C(C_2H_5)_2CN$	65	NaNH₂	Toluene	1036
		(C₂H₅)₂SO₄	$C_6H_5CH(C_2H_5)CN$	89	NaNH₂	Ether	249,359
		Cl(CH₂)₂Br	1-Phenylcyclopropane-1-carbonitrile	44	NaNH₂	Ether	305
		Br(CH₂)₂Br	1-Phenylcyclopropane-1-carbonitrile	38	NaNH₂	Ether	306, 305
		Br(CH₂)₂Br	1-Phenylcyclopropane-1-carbonitrile	51	NaNH₂	C₆H₆	307
		HO(CH₂)₂Cl	$HO(CH_2)_2CH(C_6H_5)CN$	39	NaNH₂	Ether	305

Note: References 577–1080 are on pp. 322–331.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R')CN

R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C_4H_9 (*Cont.*)	HO(CH₂)₃Cl	None	—	NaNH₂	Toluene	1037
	HO(CH₂)₂Br	None	—	NaNH₂	Toluene	1037
	CH₂——CH₃ (O)	HO(CH₂)₂CH(C₆H₅)CN	20	NaNH₂	Liquid NH₃	1037
C_3						
	n-C₃H₇Br	None	—	NaOH	None	270
	n-C₃H₇Br	n-C₃H₇CH(C₆H₅)CN	70–80	NaNH₂	Ether	1031, 359, 1034, 1035
	n-C₃H₇Br	(n-C₃H₇)₂C(C₆H₅)CN	60	NaNH₂	Toluene	1036
	n-C₃H₇X•	n-C₃H₇CH(C₆H₅)CN	—	Na	Liquid NH₃	1025
	n-C₃H₇I	n-C₃H₇CH(C₄H₅)CN	—	NaOH	None	279,79, 1031, 506
	i-C₃H₇Br	i-C₃H₇CH(C₆H₅)CN	70–80	NaNH₂	Ether	1034
	CH₂=CHCH₂Br	CH₂=CHCH₂CH(C₆H₅)CN	30	NaNH₂	Ether	60
	CH(CH₂)₃I	1-Phenylcyclobutane-1-carbonitrile	18	Na	Ether	92
	CH₂CHBrCH₂Br	1-Phenyl-2-methylcyclopropane-1-carbonitrile	18	NaNH₂	Ether	305
	Br(CH₂)₃Br	1-Phenylcyclobutane-1-carbonitrile	15	NaNH₂	Ether	306
	I(CH₂)₃I	1-Phenylcyclobutane-1-carbonitrile	39	—	Ether	92
C_4						
	CH₃OCH₂O(CH₂)₂Cl	[CH₃OCH₂O(CH₂)₂]₂C(C₆H₅)CN	61	NaNH₂	C₆H₆	1038, 1030
	n-C₄H₉Br	n-C₄H₉CH(C₆H₅)CN	—	NaNH₂	None	142
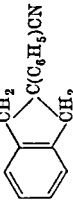
Halide	Nitrile	Yield (%)	Base	Solvent	References
$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9CH(C_6H_5)CN$	—	$NaNH_2$	Ether	350
$n\text{-}C_4H_9Br$	$(n\text{-}C_4H_9)_2C(C_6H_5)CN$	26	$NaNH_2$	Ether	566
$n\text{-}C_4H_9Br$	$(n\text{-}C_4H_9)_2C(C_6H_5)CN$	06	$NaNH_2$	Toluene	1015
$C_2H_5O(CH_2)_2Br$	$C_2H_5O(CH_2)_2CH(C_6H_5)CN$	33	$NaNH_2$	C_6H_6	1022
$C_2H_5O(CH_2)_2Br$	$[C_2H_5O(CH_2)_2]_2C(C_6H_5)CN$	54	$NaNH_2$	Toluene	500
$i\text{-}C_4H_9Br$	$i\text{-}C_4H_9CH(C_6H_5)CN$	70–80	$NaNH_2$	Ether	1031, 1034
$i\text{-}C_4H_9Br$	$(i\text{-}C_4H_9)_2C(C_6H_5)CN$	65	$NaNH_2$	Toluene	1036
$CH_2{=}CHO(CH_2)_2Cl$	$[CH_2{=}CHO(CH_2)_2]_2C(C_6H_5)CN$	76	$NaNH_2$	C_6H_6	1038, 1040
$(CH_3)_2N(CH_2)_2Cl$	$(CH_3)_2N(CH_2)_2CH(C_6H_5)CN$	80–90	$NaNH_2$	C_6H_6	178, 254, 1041, 1042
$C_2H_5CHClCH_2Cl$	1-Phenyl-2-ethylcyclopropane-1-carbonitrile	40	$NaNH_2$	Ether	258
$(CH_3)_2CClCH_2Cl$	α-Phenyl-β-isopropylacrylonitrile	38	$NaNH_2$	Ether	258
$Br(CH_2)_4Br$	1-Phenylcyclopentane-1-carbonitrile	46	$NaNH_2$	Ether	300
$Cl(CH_2)_2O(CH_2)_2Cl$	4-Phenyltetrahydropyran-4-carbonitrile	49	$NaNH_2$	Toluene	77, 499
$Cl(CH_2)_2S(CH_2)_2Cl$	4-Phenyltetrahydrothiapyran-4-carbonitrile	47	$NaNH_2$	Toluene	77, 499
$Cl(CH_2)_2NH(CH_2)_2Cl$	4-Phenylpiperidine-4-carbonitrile	Poor	$NaNH_2$	Toluene	505
C_5					
$n\text{-}C_5H_{11}I$	$n\text{-}C_5H_{11}CH(C_6H_5)CN$	—	NaOH	None	279
$n\text{-}C_5H_{11}X^*$	$n\text{-}C_5H_{11}CH(C_6H_5)CN$	—	Na	Liquid NH_3	1025
$CH_2(OCH_2CH_2Cl)_2$	$CH_2[OCH_2CH_2CH(C_6H_5)CN]_2$	65	$NaNH_2$	Toluene	1037
$Br(CH_2)_3Br$	1-Phenylcyclohexano-1-carbonitrile	58	$NaNH_2$	Ether	307, 306
$CH_3N((CH_2)_2Cl)_2$	1-Methyl-4-phenylpiperidine-4-carbonitrile	66	$NaNH_2$	Toluene	77, 503, 505

Note: References 577–1080 are on pp. 322–331.
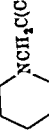
* The halogen was not specified.

TABLE XIV—Continued
ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
H	C_6H_5 (Cont.)	Cyclopentyl bromide	(α-Cyclopentyl)phenyl-acetonitrile	—	$NaNH_2$	Ether	1043
		2-Chloropyridine	Phenyl-(2-pyridyl)acetonitrile	70	$NaNH_2$	Toluene	1044
		4-Chloropyridine	Phenyl-(4-pyridyl)acetonitrile	—	$NaNH_2$	Toluene	1044
		C_6					
		$n\text{-}C_6H_{13}Br$	$n\text{-}C_6H_{13}CH(C_6H_5)CN$	—	KOH	None	77
		$n\text{-}C_6H_{13}I$	$n\text{-}C_6H_{13}CH(C_6H_5)CN$	—	NaOH	None	279
		$(C_2H_5O)_2CHCH_2Br$	$(C_2H_5O)_2CHCH_2CH(C_6H_5)CN$	38	$NaNH_2$	Ether	188
		$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2CH(C_6H_5)CN$	74	$NaNH_2$	Ether	1007
		$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2CH(C_6H_5)CN$	80–90	$NaNH_2$	C_6H_6	178,77
		$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2CH(C_6H_5)CN$	—	$NaNH_2$	Toluene	1041
		Cyclohexyl bromide	(α-Cyclohexyl)phenyl-acetonitrile	—	$NaNH_2$	Ether	1045
		Cyclohexyl bromide	(α-Cyclohexyl)phenyl-acetonitrile	72	$NaNH_2$	C_6H_6	171,1016
		Cyclohexyl bromide	(α-Cyclohexyl)phenyl-acetonitrile	05–77	$NaNH_2$	Toluene	576
		2-Cyclohexenyl bromide	Phenyl-(2-cyclohexenyl)-acetonitrile	53	$NaNH_2$	Toluene	192
		2-Bromo-3-methyl-pyridine	Phenyl-(3-methyl-2-pyridyl)-acetonitrile	08	$NaNH_2$	Toluene	254
		C_7					
		$n\text{-}C_7H_{15}I$	$n\text{-}C_7H_{15}CH(C_6H_5)CN$	—	NaOH	None	279
		$i\text{-}C_3H_7CHBrCO_2C_2H_5$	$C_2H_5O_2CCH(C_3H_7\text{-}i)CH(C_6H_5)CN$	—	$NaNH_2$	Ether	1047
		$CH_3N(CH_2CHClCH_3)_2$	1,3,5-Trimethyl-4-phenylpiperidine-4-carbonitrile	39	$NaNH_2$	Toluene	505
		$CH_3N(CH_2CHClCH_3)_2$	1,3,5-Trimethyl-4-phenylpiperidine-4-carbonitrile	41	KNH_2	Toluene	503

Halide	Nitrile (product)	Base	Yield (%)	Solvent	References
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CN$	NaOH	55	None	34
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CN$	NaOH	50	$(C_2H_5)_3N \cdot H_2O$	84
$C_6H_5CH_2Cl$	None	NaOH	—	$(i\text{-}C_3H_7)_2NC_2H_5 \cdot H_2O$	84
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CN$	$NaOCH_3$	13	CH_3OH	34
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CN$	$NaOC_2H_5$	33	Ethanol	34, 1001, 1048
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CN$	$NaOC_3H_7\text{-}n$	28	$n\text{-}C_3H_7OH$	34
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CN$	$NaOC_5H_{11}\text{-}n$	Poor	$n\text{-}C_5H_{11}OH$	34
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH(C_6H_5)CN$	$NaNH_2$	34	Ether	566
$C_6H_5CH_2Cl$	$\{C_6H_5CH(C_6H_5)CN$; $(C_6H_5CH_2)_2C(C_6H_5)CN\}$	$NaNH_2$	33 ; 30	Liquid-NH_3-ether	195
$C_6H_5CH_2Br$	$C_6H_5CH_2CH(C_6H_5)CN$	$NaOC_2H_5$	—	Ethanol	34
$C_6H_5CH_2I$	$C_6H_5CH_2CH(C_6H_5)CN$	$NaOC_2H_5$	—	Ethanol	34
$C_6H_5CHCl_2$	$C_6H_5CH{=}C(C_6H_5)CN$	NaOH	—	None	564
C_8					
$n\text{-}C_8H_{17}I$	$n\text{-}C_8H_{11}CH(C_6H_5)CN$	NaOH	—	None	279
$C_6H_5CH(CH_3)Cl$	$C_6H_5CH(CH_3)CH(C_6H_5)CN$	KNH_2	99	Liquid NH_3-ether	195
$\begin{array}{c}\text{CH}_2\text{Br}\\ \text{CH}_2\text{Br}\end{array}$ (o-xylylene dibromide)	indane-$C(C_6H_5)CN$ structure	$NaNH_2$	8	Ether	300
C_9					
$C_6H_5O(CH_2)_3Br$	$C_6H_5O(CH_2)_3CH(C_6H_5)CN$	$NaNH_2$	63	Ether	1049
$CH_2[O(CH_2)_2Cl]_2$	$CH_2[O(CH_2)_2CH(C_6H_5)CN]_2$	$NaNH_2$	23	Toluene	1037
4-Chloroquinoline	Phenyl-(4-quinolyl)acetonitrile	$NaNH_2$	76	C_6H_6	178
4,5-Dichloroquinoline	Phenyl-(5-chloro-4-quinolyl)-acetonitrile	$NaNH_2$	100	C_6H_6	178
4,7-Dichloroquinoline	Phenyl-(7-chloro-4-quinolyl)-acetonitrile	$NaNH_2$	90	C_6H_6	178
C_{10}					
$C_6H_5CH_2N(CH_3)(CH_2)_2Cl$	$C_6H_5CH_2N(CH_3)(CH_2)_2\text{-}CH(C_6H_5)CN$	$NaNH_2$	68	Ether	188
cyclo-$C_6H_{11}N(CH_2CH_2Cl)_2$	1-Cyclohexyl-4-phenyl-piperidine-4-carbonitrile	$NaNH_2$	61	Toluene	503, 505
$C_6H_5N(CH_2CH_2Cl)_2$	1,4-Diphenylpiperidine-4-carbonitrile	$NaNH_2$	60	Toluene	503, 505

Note: References 577–1080 are on pp. 322–331.

TABLE XIV—Continued

ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
H	C₆H₅ (Cont.)	C_{11}–C_{13}					
		C₆H₅CH₂N(CH₂CH₂Cl)₂	1-Benzyl-4-phenylpiperidine-4-carbonitrile	65	NaNH₂	Toluene	505, 77, 503, 1037
		3-Phthalimidopropyl bromide	None	—	—	—	77
		p-CH₃C₆H₄SO₂-N(CH₂CH₂Cl)₂	p-CH₃C₆H₄SO₂-N(ring) C(CN)C₆H₅ (CH₂CH₂)₂	37	NaNH₂	Toluene	
H	o-ClC₆H₄	(C₆H₅)₂CHCl	(C₆H₅)₂CHCH(C₆H₅)CN	99	KNH₂	Liquid NH₃-ether	195
		(CH₃)₂N(CH₂)₂Cl	(CH₃)₂N(CH₂)₂CH(C₆H₄Cl-o)CN	58	NaNH₂	C₆H₆	254
		2-Bromopyridine	o-Chlorophenyl-(2-pyridyl)-acetonitrile	42	NaNH₂	Toluene	254
H	p-ClC₆H₄	(CH₃)₂N(CH₂)₂Cl	(CH₃)₂N(CH₂)₂CH(C₆H₄Cl-p)CN	60	NaNH₂	C₆H₆	251
		2-Bromopyridine	p-Chlorophenyl-(2-pyridyl)-acetonitrile	73	NaNH₂	Toluene	254
		(C₂H₅)₂N(CH₂)₂Cl	(C₂H₅)₂N(CH₂)₂-CH(C₆H₄Cl-p)CN	64	NaNH₂	Toluene	1042, 1011
		(C₂H₅)₂N(CH₂)₃Cl	(C₂H₅)₂N(CH₂)₃-CH(C₆H₄Cl-p)CN	58	NaNH₂	C₆H₆	1042, 1011
H	3,4-Dichlorophenyl	(C₂H₅)₂N(CH₂)₂Cl	(C₂H₅)₂N(CH₂)₂-CH(C₆H₃Cl₂-3,4)CN	43	NaNH₂	C₆H₆	1042, 1041
H	NCH₂ (ring)	n-C₄H₉Br	NCH₂C(C₄H₉-n)₂CN	93	NaNH₂	Toluene	1015
H	C₆H₅CH₂	(CH₃)₂N(CH₂)₂Cl	(CH₃)₂N(CH₂)₂CH(CH₂C₆H₅)CN	54	NaNH₂	Toluene	254
H	o-CH₃C₆H₄	CH₂=CHO(CH₂)₂Cl	[CH₂=CHO(CH₂)₂]-C(C₆H₄CH₃-o)CN	—	NaNH₂	Toluene	1038
H	o-CH₃OC₆H₄	CH₃N(CH₂CH₂Cl)₂	1-Methyl-4-(2'-methoxyphenyl)-piperidine-4-carbonitrile	—	NaNH₂	Toluene	190

	R	Halide	Nitrile (product)	Yield, %	Condensing agent	Solvent	References
II	m-CH₃OC₆H₄	Cyclohexyl bromide	Cyclohexyl-(o-methoxyphenyl)-acetonitrile	05	NaNH₂	C₆H₆	1007, 1008
II		CH₃N(CH₂CH₂Cl)₂	1-Methyl-4-(3'-methoxyphenyl)-piperidine-4-carbonitrile	—	—	—	501
II	p-CH₃C₆H₄	(CH₃)₂N(CH₂)₂Cl	(CH₃)₂N(CH₂)₂-CH(C₆H₄CH₃-p)CN	79	NaNH₂	C₆H₆	254
II	p-CH₃OC₆H₄	CH₃N(CH₂CH₂Cl)₂	1-Methyl-4-(4'-methoxyphenyl)-piperidine-4-carbonitrile	63	NaNH₂	Toluene	503, 505
II		(C₂H₅)₂N(CH₂)₂Cl	(C₂H₅)₂N(CH₂)₂-CH(C₆H₄OCH₃-p)CN	70	NaNH₂	C₆H₆	1042, 1041
II	2-Methoxy-5-methylphenyl	n-C₃H₇Br	n-C₃H₇-CH(C₆H₃(OCH₃)(CH₃)-2,5)CN	92	NaNH₂	C₆H₆	1007, 1008
II		(C₂H₅)₂N(CH₂)₂Cl	(C₂H₅)₂N(CH₂)₂ CH[C₆H₃(OCH₃)(CH₃)-2,5]CN	83	NaNH₂	C₆H₆	1007, 1008
II	3,4-Dimethoxy-phenyl	CH₃N(CH₂CH₂Cl)₂	1-Methyl-4-(3',4'-dimethoxy-phenyl)piperidine-4-carbonitrile	—	NaNH₂	Toluene	190
II	n-C₉H₁₉	n-C₈H₁₇Br	n-C₉H₁₉CH(C₈H₁₇-n)CN	25	NaNH₂	C₆H₆	289
II	α-Naphthyl	(CH₃)₂N(CH₂)₂Cl	(CH₃)₂N(CH₂)₂OH(C₁₀H₇-α)CN	75	NaNH₂	C₆H₆	254
II		CH₃N(CH₂CH₂Cl)₂	1-Methyl-4-(α-naphthyl)-piperidine-4-carbonitrile	50	NaNH₂	Toluene	503
II		2-Chloropyridine	2-Pyridyl-(α-naphthyl)-acetonitrile	—	NaNH₂	Toluene	1044
II	o-Benzyloxyphenyl	CH₃N(CH₂CH₂Cl)₂	1-Methyl-4-(o-benzyloxy-phenyl)piperidine-4-carbonitrile	—	NaNH₂	Toluene	190
	n-C₁₆H₃₃	CH₃I	n-C₁₆H₃₃C(CH₃)₂CN	30	LiN(C₂H₅)₂	Ether	65
CH₃	CH₃	CH₃O(CH₂)₂Br	CH₃O(CH₂)₂C(CH₃)₂CN	54	NaNH₂	C₆H₆	53, 122
		CH₂=CHCH₂Cl	CH₂=CHCH₂C(CH₃)₂CN	70	LiNH₂	Ether	53
		CH₂=CHCH₂Cl	CH₂=CHCH₂C(CH₃)₂CN	Good	NaNH₂	None	122
		CH₂=CHCH₂Cl	CH₂=CHCH₂C(CH₃)₂CN	—	NaNH₂	Inert solvent	1013
		CH₂=CHCH₂Cl	CH₂=CHCH₂C(CH₃)₂CN	83	NaN(C₂H₅)₂	Ether	53
		CH₂=CHCH₂Br	CH₂=CHCH₂C(CH₃)₂CN	61	BrMgN(C₂H₅)₂	Ether	53
		Cl(CH₂)₃Br	Cl(CH₂)₃C(CH₃)₂CN	—	NaNH₂	C₆H₆	122
		C₆H₅CH₂Cl	None	—	NaOC₂H₅	Ethanol	1017
		C₆H₅CH₂Cl	C₆H₅CH₂C(CH₃)₂CN	Good	NaH	Toluene	122, 66
		C₆H₅CH₂Cl	C₆H₅CH₂C(CH₃)₂CN	97	LiN(C₂H₅)₂	Ether	255
C₂H₅	C₂H₅	C₂H₅Br	(C₂H₅)₃CCN	31	Na	Ether	1050

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R′)CN
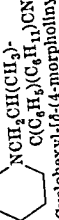
R	R′	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
	C_2H_5 (*Cont.*)	$(C_2H_5)_2SO_4$	$(C_2H_5)_3CCN$	—	$LiNC_5H_{10}$ (piperidide)	Ether	255
		$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	81	$LiNC_5H_{10}$ (piperidide)	Ether	255
		$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	60	$LiNHC_6H_{11}$	Ether	53
		$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	91	NaC_6H_5	C_6H_6	90
		$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	ca.100	$NaNH_2$	C_6H_6	53, 122, 1013
		$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	88	$NaN(C_2H_5)_2$	Ether	53
		$CH_2{=}CHCH_2Cl$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	—	Na	Xylene	1050
		$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	—	K	Ether	1050
		$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	—	K	C_6H_6	1050
		$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	—	Cu	Toluene	1051
		$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	78	$BrMgN(C_6H_{11})_2$	Ether	1013
		$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	80	$NaNH_2$	C_6H_6	53, 122
		$CH_2{=}CHCH_2I$	$CH_2{=}CHCH_2C(C_2H_5)_2CN$	73	$NaNH_2$	C_6H_6	53, 122
		$n\text{-}C_4H_9Br$	$n\text{-}C_4H_9C(C_2H_5)_2CN$	—	$NaNH_2$	C_6H_6	1050
		$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2C(C_2H_5)_2CN$	—	K	Ether	59
		$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_2H_5)_2CN$	—	$NaNH_2$	Ether	122
		$C_2H_5CH_2Cl$	$C_2H_5CH_2C(C_2H_5)_2CN$	—	$NaNH_2$	C_6H_6	53, 122, 1013
		$i\text{-}C_3H_7Cl$	$(i\text{-}C_3H_7)C(C_2H_5)_2CN$	—	$NaNH_2$	C_6H_6	1050
C_2H_5	$i\text{-}C_3H_7$	$CH_2{=}CHCH_2Br$	α-Allyl-α-isopropylbutyronitrile	44	K	C_6H_6	90
		$CH_2{=}CHCH_2Cl$	$(CH_2{=}CHCH_2)C(C_2H_5)_2CN$	73	NaC_6H_5	C_6H_6	90
		$CH_2{=}CHCH_2Cl$	α-Allyl-α-ethylcapronitrile	60	$BrMgN(C_6H_{11})_2$	Inert solvent	255
		C_2H_5I	$(CH_2{=}CHCH_2)C(C_2H_5)_2CS$	83	NaC_6H_5	C_6H_6-ligroin	90
C_2H_5	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2Cl$	$(CH_2{=}CHCH_2)_3CCS$	—	$BrMgN(C_6H_{11})_2$	Inert solvent	255
C_2H_5	$n\text{-}C_4H_9$	$CH_2{=}CHCH_2Cl$	$(CH_2{=}CHCH_2)_2CCN$	—	K	Ether	1050
$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2Br$	$(CH_2{=}CHCH_2)_3CCN$	—	$BrMgN(C_6H_{11})_2$	Inert solvent	255
		$i\text{-}C_3H_7Cl$	$(CH_2{=}CHCH_2)_2C(i\text{-}C_3H_7)CN$	79	NaC_6H_5	C_6H_6	90

Nitrile	Halide	Product	Yield (%)	Base	Solvent	References
†	$C_6H_5CH_2Cl$	[cyclohexene] $(CN)CH_2C_6H_5$, CH_3	Good	$NaNH_2$	C_6H_6	122
CH_3	$Cl(CH_2)_2Cl$	$Cl(CH_2)_2C(CH_3)(C_6H_5)CN$	20	$NaNH_2$	C_6H_6	359, 1023, 501
	$(CH_3)_2N(CH_2)_2Cl$	$(CH_2)_2N(CH_2)_2\text{-}C(CH_3)(C_6H_5)CN$	66	$NaNH_2$	Toluene	
	$CH_3CHBrCO_2C_2H_5$	$C_2H_5O_2CC(CH_3)\text{-}C(CH_3)(C_6H_5)CN$	15	$NaNH_2$	Ether	583
C_2H_5	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(CH_3)(C_6H_5)CN$	—	$NaOC_2H_5$	Ethanol	34
	C_2H_5I	$C_6H_5C(C_2H_5)_2CN$	—	Na	Ether	1052
	C_2H_5I	$C_6H_5(C_2H_5)_2CN$	75	$NaNH_2$	Ether	1035
	$Cl(CH_2)_2Cl$	$Cl(CH_2)_2C(C_2H_5)(C_6H_5)CN$	53	$NaNH_2$	C_6H_6	1032, 359
	Cyclopentyl bromide	α-Phenyl-α-cyclopentyl-butyronitrile	—	$NaNH_2$	Ether	1043
	2-Chloropyridine	α-Ethyl-α-phenyl-α-(2-pyridyl)-acetonitrile	—	$NaNH_2$	Toluene	1044
	$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2\text{-}C(C_2H_5)(C_6H_5)CN$	67	$NaNH_2$	Toluene	190
$Cl(CH_2)_2$	None	1-Phenylcyclopropane-1-carbonitrile	73	$NaNH_2$	Liquid NH_3	305
$C_6H_5CH_2$ [thiophene]	CH_3I	$C_6H_5CH_2C(CH_3)(C_6H_5)CN$	—	$NaNH_2$	Ether	1018
$(CH_3)_2N(CH_2)_2$	2-Bromopyridine	$(CH_3)_2N(CH_2)_2\text{-}C(C_4H_5S)(C_5H_4,N\text{-}2)CN$	36	$NaNH_2$	Toluene	254
C_6H_5	$Cl(CH_2)_2Cl$	$Cl(CH_2)_2C(C_6H_5)(C_3H_7\text{-}n)CN$	24	$NaNH_2$	C_6H_6	359
$n\text{-}C_3H_7$	$i\text{-}C_4H_9Br$	$i\text{-}C_4H_9CC(C_6H_5)(C_3H_7\text{-}n)CN$	75	$NaNH_2$	Ether	1035
	$Br(CH_2)_2CO_2C_2H_5$	$C_2H_5O_2C(CH_2)_2\text{-}C(C_3H_7\text{-}n)(C_6H_5)CN$	75	$NaNH_2$	C_6H_6	1053
C_6H_5	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_6H_5)(C_3H_7\text{-}n)CN$	—	NaOH	None	279
$(CH_3)_2N(CH_2)_2$	2-Bromopyridine	$(CH_3)_2N(CH_2)_2\text{-}C(C_5H_4,N\text{-}2)(C_5H_4,N\text{-}3)CN$	35	$NaNH_2$	Toluene	254
$n\text{-}C_4H_9$	$Cl(CH_2)_2Cl$	$Cl(CH_2)_2C(C_6H_5)(C_4H_9\text{-}n)CN$	—	$NaNH_2$	C_6H_6	359

Note: References 577–1030 are on pp. 322–331.

† The nitrile alkylated was [structure: cyclohexene ring bearing CN and CH_3].

TABLE XIV—Continued

ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield %	Base	Solvent	Reference
n	C_6H_5	$(CH_3)_2N(CH_2)_2Cl\cdot HCl$	$(CH_3)_2N(CH_2)_2C(C_6H_5)(C_4H_9\text{-}i)CN$	68	$NaNH_2$	C_6H_6	101
i-C_4H_9		$(C_2H_5)_2N(CH_2)_2Cl\cdot HCl$	$(C_2H_5)_2N(CH_2)_2C(C_4H_9\text{-}i)CN$	81	$NaNH_2$	C_6H_6	101
		β-(1-Piperidyl)ethyl chloride hydrochloride	α-(i-Butyl)-α-phenyl-γ-(1-piperidyl)butyronitrile	79	$NaNH_2$	C_6H_6	191
		β-(1-Piperidyl)ethyl chloride hydrochloride	α-(i-butenyl)-α-phenyl-γ-(1-piperidyl)butyronitrile	75	$NaNH_2$	C_6H_6	191
$(CH_3)_2C=CH$	C_6H_5	β-(1-Piperidyl)ethyl chloride hydrochloride	α-(2-Methylallyl)-α-phenyl-γ-(1-piperidyl)butyronitrile	72	$NaNH_2$	C_6H_6	191
$CH_2=C(CH_3)CH_2$	C_6H_5	2-Bromopyridine	$(CH_3)_2N(CH_2)_2C(C_6H_{11}\text{-}cyclo)(C_5H_4N\text{-}2)CN$	50	$NaNH_2$	Toluene	254
$(CH_3)_2N(CH_2)_2$	cyclo-C_6H_{11}	2-Bromopyridine	$(CH_3)_2N(CH_2)_2C(C_5H_4N\text{-}2)_2$	78	$NaNH_2$	Toluene	254
$(CH_3)_2N(CH_2)_2$	C_6H_5	2-Bromopyridine	$(CH_3)_2N(CH_2)_2C(C_5H_4N\text{-}2)(C_6H_5)CN$	76	$NaNH_2$	Toluene	254
		4-Bromopyridine	$(CH_3)_2N(CH_2)_2C(C_5H_4N\text{-}4)(C_6H_5)CN$	82	$NaNH_2$	Toluene	254
		Cyclo-$C_6H_{11}Br$	$(CH_3)_2N(CH_2)_2C(C_6H_{11}\text{-}cyclo)CN$	74	$NaNH_2$	Toluene	254
		2-Bromo-6-methylpyridine	α-Phenyl-α-(6-methyl-2-pyridyl)-γ-(dimethylamino)butyronitrile	88	$NaNH_2$	C_6H_6	178
		4-Chloroquinoline	$(CH_3)_2N(CH_2)_2C(C_9H_6N\text{-}4)CN$	86	$NaNH_2$	C_6H_6	178
		4,5-Dichloroquinoline	α-Phenyl-α-(5-chloro-4-quinolyl)-γ-(dimethylamino)butyronitrile	95,	$NaNH_2$	C_6H_6	178
		4,7-Dichloroquinoline	α-Phenyl-α-(7-chloro-4-quinolyl)-γ-(dimethylamino)butyronitrile	67	$NaNH_2$	Toluene	254
$(CH_3)_2N(CH_2)_2$	p-ClC_6H_4	2-Bromopyridine	$(CH_3)_2N(CH_2)_2C(C_6H_4N\text{-}2)(C_6H_4Cl\text{-}p)CN$	90	$NaNH_2$	Toluene	254
(thiophene)	cyclo-C_6H_{11}	$(CH_3)_2N(CH_2)_2Cl$	$(CH_3)_2N(CH_2)_2C(C_4H_3S)(C_6H_{11}\text{-}cyclo)CN$				1023

Substrate	Alkylating agent	Product	Yield (%)	Condensing agent	Solvent	Reference
(structure)	$(CH_3)_2N(CH_2)_2Cl$	$(CH_3)_2N(CH_2)_2C(C_5H_4N\text{-}2)_2CN$	78	$NaNH_2$	Toluene	254
CH_3	$n\text{-}C_{10}H_{21}Br$	$(n\text{-}C_{10}H_{21})_2C(CH_3)CN$	—	—	Toluene	289
$n\text{-}C_3H_7$	$(C_2H_5)_2N(CH_2)_2Cl$	$\alpha\text{-}(2\text{-Diethylaminoethyl})\text{-}\alpha\text{-}(2\text{-methoxy-5-methylphenyl})valeronitrile$	70	$NaNH_2$	C_6H_6	1007, 1008
2-Methoxy-5-methylphenyl	2-Bromopyridine	$(CH_3)_2N(CH_2)_2\text{-}C(CH_2C_6H_5)(C_5H_4N\text{-}2)CN$	41	$NaNH_2$	Toluene	254
$C_2H_5CH_2$	2-Bromopyridine	$(CH_3)_2N(CH_2)_2\text{-}C(C_6H_4CH_3\text{-}p)(C_5H_4N\text{-}2)CN$	44	$NaNH_2$	Toluene	254
$p\text{-}ClH_3C_6H_4$	2-Bromopyridine	$(CH_3)_2N(CH_2)_2\text{-}C(C_6H_4OCH_3\text{-}p)(C_5H_4N\text{-}2)CN$	80	$NaNH_2$	Toluene	254
$p\text{-}CH_3OC_6H_4$	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_6H_4)(C_5H_{11}\text{-}n)CN$	—	$NaOH$	None	279
$n\text{-}C_5H_{11}$, $cyclo\text{-}C_5H_9$	$(CH_3)_2N(CH_2)_2Cl\cdot HCl$	$(CH_3)_2N(CH_2)_2\text{-}C(C_6H_5)(C_5H_9\text{-}2)CN$	73	$NaNH_2$	C_6H_6	191
	Cyclopentyl bromide	$C_6H_5C(C_5H_9\text{-}2)CN$	—	$NaNH_2$	Ether	1043
C_6H_5	C_2H_5Br	$C_6H_5C(C_2H_5)(C_5H_4N\text{-}2)CN$	85	$NaNH_2$	Toluene	1044
	$(CH_3)_2N(CH_2)_2Cl$	$(CH_3)_2N(CH_2)_2\text{-}C(C_6H_4N\text{-}2)CN$	74	$NaNH_2$	Toluene	254
	$(CH_3)_2N(CH_2)_3Cl$	$(CH_3)_2N(CH_2)_3\text{-}C(C_6H_5)(C_5H_4N\text{-}2)CN$	82	$NaNH_2$	Toluene	254
	$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2\text{-}C(C_6H_5)(C_5H_4N\text{-}2)CN$	92	$NaNH_2$	Toluene	254
	$\beta\text{-}(1\text{-Piperidyl})ethyl$ chloride	$\alpha\text{-Phenyl-}\alpha\text{-}(2\text{-pyridyl})\text{-}\gamma\text{-}(1'\text{-piperidyl})butyronitrile$	89	$NaNH_2$	Toluene	254
$o\text{-}ClC_6H_4$	$(CH_3)_2N(CH_2)_2Cl$	$(CH_3)_2N(CH_2)_2\text{-}C(C_6H_4Cl\text{-}o)(C_5H_4N\text{-}2)CN$	33	$NaNH_2$	Toluene	254
$C_6H_5CH_2$	$(CH_3)_2NCH_2Cl$	$(CH_3)_2NCH_2\text{-}C(C_6H_4C_2H_5)(C_5H_4N\text{-}2)CN$	46	$NaNH_2$	Toluene	254
$n\text{-}C_6H_{13}$	$(C_2H_5)_2N(CH_2)_2Cl$	$(C_2H_5)_2N(CH_2)_2\text{-}C(C_6H_5)(C_6H_{13}\text{-}n)CN$	75	$NaNH_2$	Toluene	77, 191
$(C_2H_5)_2N(CH_2)_2$	$C_6H_5CH_2Cl$	None	—	$NaOH$	None	279
C_6H_5	Cyclohexene oxide	$\gamma\text{-Diethylamino-}\alpha\text{-}(2\text{-hydroxycyclohexyl})\text{-}\alpha\text{-phenylbutyronitrile}$	—	$NaNH_2$	Ether	1007
	4-Chloroquinoline	$(C_2H_5)_2N(CH_2)_2\text{-}C(C_6H_5)(C_9H_6N\text{-}4)CN$	97	$NaNH_2$	C_6H_6	178

TABLE XIV—Continued

ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield %	Base	Solvent	Reference
$(C_2H_5)_2N(CH_2)_2$	C_6H_5 (Cont.)	4,5-Dichloroquinoline	α-Phenyl-α-(5-chloro-4-quinolyl)-γ-(diethylamino)butyronitrile	98	$NaNH_2$	C_6H_6	178
		4,7-Dichloroquinoline	α-Phenyl-α-(7-chloro-4-quinolyl)-γ-(diethylamino)butyronitrile	91	$NaNH_2$	C_6H_6	178
Cyclohexyl (=C_6H_{11})	C_6H_5	CH_3X†	$C_6H_5C(CH_3)(C_6H_{11})CN$	— / 94	$NaNH_2$ / $NaNH_2$ / $NaNH_2$	Ether / C_6H_6 / Liquid NH_3	1054 / 1004 / 171
		C_2H_5Br	$C_6H_5C(C_2H_5)(C_6H_{11})CN$	70	$NaNH_2$	C_6H_6	101, 1055
		$n\text{-}C_3H_7I$	$n\text{-}C_3H_7C(C_6H_5)(C_6H_{11})CN$	72	$NaNH_2$	C_6H_6	1055
		$(CH_3)_2N(CH_2)_2Cl\cdot HCl$	$(CH_3)_2N(CH_2)_2\text{-}C(C_6H_5)(C_6H_{11})CN$	—	$NaNH_2$	C_6H_6	1055
		$(CH_3)_2NCH_2CH(CH_3)Br$	$(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)(C_6H_{11})CN$	—	$NaNH_2$	Ether	1043
		$(CH_3)_2NCH(CH_3)CH_2Br$	$(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)(C_6H_{11})CN$	—	$NaNH_2$	C_6H_6	191, 1055
		Cyclopentyl bromide	Cyclopentyl(cyclohexyl)phenyl-acetonitrile	82	$NaNH_2$	C_6H_6	191
		$(C_2H_5)_2N(CH_2)_2Cl\cdot HCl$	$(C_2H_5)_2N(CH_2)_2\text{-}C(C_6H_5)(C_6H_{11})CN$	90	$NaNH_2$	C_6H_6	1055
		β-(1-Pyrrolidyl)ethyl chloride hydrochloride $(C_2H_5)_3NCH(C_2H_5)Cl$	α-Cyclohexyl-α-phenyl-γ-(1-pyrrolidyl)butyronitrile $(C_2H_5)_2NCH(C_2H_5)\text{-}C(C_6H_5)(C_6H_{11})CN$	—	$NaNH_2$	C_6H_6	191
		β-(1-Piperidyl)ethyl chloride hydrochloride $(C_2H_5)_2NCHC_2H_5)CH_2Cl$	α-Cyclohexyl-α-phenyl-γ-(1-piperidyl)butyronitrile $(C_2H_5)_2NCH(C_2H_5)CH_2\text{-}C(C_6H_5)(C_6H_{11})CN$	82	$NaNH_2$	C_6H_6	1055
		(4-morpholinyl)$NCH_2CH(CH_3)Cl$	(4-morpholinyl)$NCH_2CH(CH_3)\text{-}C(C_6H_5)(C_6H_{11})CN$	—	$NaNH_2$	C_6H_6	1055
		δ-(4-Morpholinyl)butyl chloride $(C_2H_5)_2NCH_2C(CH_3)_2CH_2Cl$	Cyclohexyl-[δ-(4-morpholinyl)butyl]phenylacetonitrile $(C_2H_5)_2NCH_2C(CH_3)_2\text{-}CH_2C(C_6H_5)(C_6H_{11})CN$	—	$NaNH_2$	C_6H_6	1055

Alkylating agent	Product	Yield (%)	Condensing agent	Solvent	Reference
$(n\text{-}C_4H_9)_2N(CH_2)_3Cl$	$(n\text{-}C_4H_9)_2N(CH_2)_3\text{-}C(C_6H_5)(C_6H_{11})CN$	—	$NaNH_2$	C_6H_6	1055
$(C_2H_5)_2N(CH_2)_2Cl$	$\beta\text{-[Diethylaminoethyl]-(1-cyclohexenyl)phenyl-acetonitrile}$	31	$NaNH_2$	Toluene	1056
I_2	$(C_6H_5)_2C(CN)C(C_6H_5)_2CN$	100	$NaOC_2H_5$	Ethanol	264
C_2					
C_2H_5I	$(C_6H_5)_2C(C_2H_5)CN$	88	$NaNH_2$	C_6H_6	1004
$Cl(CH_2)_2Cl$	$\left\{ \begin{array}{l} Cl(CH_2)_2C(C_6H_5)_2CN \\ NCC(C_6H_5)_2(CH_2)_2C(C_6H_5)_2CN \end{array} \right.$	70 / —	$NaNH_2$	C_6H_6	1057
$Br(CH_2)_2Br$	$Br(CH_2)_2C(C_6H_5)_2CN$	74–80	$NaNH_2$	C_6H_6	1057, 91
$CH_2\!-\!CH_2$ (epoxide, O)	None	—	$NaOC_2H_5$	Ethanol	25
$CH_2\!-\!CH_2$ (epoxide, O)	$CH_2CH_2C(C_6H_5)_2$ — CO — O (lactone)	52	$NaOC_2H_5$	C_6H_6	25
$CH_2\!-\!CH_2$ (epoxide, O)	$CH_2CH_2C(C_6H_5)_2$ — CO — O (lactone)	57	$NaNH_2$	C_6H_6	25
C_3					
$n\text{-}C_3H_7I$	$n\text{-}C_3H_7C(C_6H_5)_2CN$	88	$KOC_4H_9\text{-}t$	Xylene-t-C_4H_9OH	27
$i\text{-}C_3H_7I$	$i\text{-}C_3H_7C(C_6H_5)_2CN$	72	$KOC_4H_9\text{-}t$	Xylene	27
$CH_2\!=\!CHCH_2Cl$	$CH_2\!=\!CHCH_2C(C_6H_5)_2CN$	94	$NaNH_2$	C_6H_6	25, 329
$CH_2\!=\!CHCH_2Br$	$CH_2\!=\!CHCH_2C(C_6H_5)_2CN$	72	$KOC_4H_9\text{-}t$	Xylene-t-C_4H_9OH	27
$CH_3CHClCH_2Br$	$CH_3CHClCH_2C(C_6H_5)_2CN$	47	$NaNH_2$	C_6H_6	25
$Br(CH_2)_3Br$	$Br(CH_2)_3C(C_6H_5)_2CN$	—	$NaNH_2$	C_6H_6	1057
$H_3CCH\!-\!CH_2$ (epoxide, O)	$CH_2\!-\!C(C_6H_5)_2 \cdots C=NH \cdots H_3CCH\!-\!O$ (ring)	57	$KOC_4H_9\text{-}t$	$t\text{-}C_4H_9OH$	27
$H_3CCH\!-\!CH_2$ (epoxide, O)	$CH_2\!-\!C(C_6H_5)_2 \cdots C=NH \cdots H_3CCH\!-\!O$ (ring)	80	$NaNH_2$	C_6H_6	329

First-substituent column values (at left): 1-Cyclohexenyl, C_6H_5; C_6H_5, C_6H_5; C_6H_5, C_6H_5.

Note: References 577–1080 are on pp. 322–331.
† The methylating agent was not specified.

TABLE XIV—Continued

ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield %	Base	Solvent	Reference
$(C_2H_5)_2N(CH_2)_2$	C_6H_5 (Cont.)	4,5-Dichloroquinoline	α-Phenyl-α-(5-chloro-4-quinolyl)-γ-(diethylamino)butyronitrile	98	NaNH₂	C_6H_6	178
		4,7-Dichloroquinoline	α-phenyl-α-(7-chloro-4-quinolyl)-γ-(diethylamino)butyronitrile	91	NaNH₂	C_6H_6	178
Cyclohexyl (--C_6H_{11})	C_6H_5	$CH_3X^\dagger$	$C_6H_5C(CH_3)(C_6H_{11})CN$	—	NaNH₂	Ether	1054
		C_2H_5Br	$C_6H_5C(C_2H_5)(C_6H_{11})CN$	94	NaNH₂	C_6H_6, Liquid NH₃	1004, 171
		$n\text{-}C_3H_7I$	$n\text{-}C_3H_7C(C_6H_5)(C_6H_{11})CN$	70	NaNH₂	C_6H_6	191, 1055
		$(CH_3)_2N(CH_2)_2\cdot$	$(CH_3)_2N(CH_2)_2C(C_6H_5)(C_6H_{11})CN$	72	NaNH₂	C_6H_6	1055
		$(CH_3)_2NCH_2CH(CH_3)Br$	$(CH_3)_2NCH_2CH(CH_3)\cdot C(C_6H_5)(C_6H_{11})CN$	—	NaNH₂	C_6H_6	1055
		$(CH_3)_2NCH(CH_3)CH_2Br$	$(CH_3)_2NCH(CH_3)CH_2\cdot C(C_6H_5)(C_6H_{11})CN$	—	NaNH₂	Ether	1043
		Cyclopentyl bromide	Cyclopentyl(cyclohexyl)phenyl-acetonitrile	—	NaNH₂	C_6H_6	191, 1055
		$(C_2H_5)_2N(CH_2)_2Cl\cdot HCl$	$(C_2H_5)_2N(CH_2)_2\cdot C(C_6H_5)(C_6H_{11})CN$	82	NaNH₂	C_6H_6	191
		β-(1-Pyrrolidyl)ethyl chloride hydrochloride $(C_2H_5)_2NCH(C_2H_5)Cl$	α-Cyclohexyl-α-phenyl-γ-(1-pyrrolidyl)butyronitrile $(C_2H_5)_2NCH(C_2H_5)\cdot C(C_6H_5)(C_6H_{11})CN$	90	NaNH₂	C_6H_6	1055
				—	NaNH₂	C_6H_6	191
		β-(1-Piperidyl)ethyl chloride hydrochloride $(C_2H_5)_2NCH(C_2H_5)CH_2Cl$	α-Cyclohexyl-α-phenyl-γ-(1-piperidyl)butyronitrile $(C_2H_5)_2NCH(C_2H_5)CH_2\cdot C(C_6H_5)(C_6H_{11})CN$	82	NaNH₂	C_6H_6	1055
		![ring]NCH₂CH(CH₃)Cl	NCH₂CH(CH₃)·C(C₆H₅)(C₆H₁₁)CN	—	NaNH₂	C_6H_6	1055
		δ-(4-Morpholinyl)butyl chloride $(C_2H_5)_2NCH_2C(CH_3)_2\cdot CH_2Cl$	Cyclohexyl-[δ-(4-morpholinyl)butyl]phenylacetonitrile $(C_2H_5)_2NCH_2C(CH_3)_2\cdot CH_2C(C_6H_5)(C_6H_{11})CN$	—	NaNH₂	C_6H_6	1055

R	Alkylating agent	Product	% Yield	Condensing agent	Solvent	References
1-Cyclohexenyl	(n-C₄H₉)₂N(CH₂)₂Cl	(n-C₄H₉)₂N(CH₂)₃-C(C₆H₅)(C₆H₁₁)CN	—	NaNH₂	C₆H₆	1055
	(C₂H₅)₂N(CH₂)₂Cl	β-[(Diethylamino)ethyl]-(1-cyclohexenyl)phenyl-acetonitrile	31	NaNH₂	Toluene	1056
C₆H₅	I₂	(C₆H₅)₂C(CN)C(C₆H₅)₂CN	100	NaOC₂H₅	Ethanol	264
C₂						
C₄H₅	C₂H₅I	(C₂H₅)₂C(C₂H₅)CN	88	NaNH₂	C₆H₆	1004
	Cl(CH₂)₂Cl	{ Cl(CH₂)₂C(C₆H₅)₂CN / NCC(C₆H₅)₂(CH₂)₂C(C₆H₅)₂CN }	70	NaNH₂	C₆H₆	1057
	Br(CH₂)₂Br	Br(CH₂)₂C(C₆H₅)₂CN	—	NaNH₂	C₆H₆	1057, 91
	CH₂——CH₂ \O/	None	74–80	NaNH₂ / NaOC₂H₅	C₆H₆ / Ethanol	25
	CH₂——CH₂ \O/	C'H₂CH₂C(C₆H₅)₂—O—CO (cyclic)	52	NaOC₂H₅	C₆H₆	25
	CH₂——CH₂ \O/	CH₂CH₂C(C₆H₅)₂—O—CO (cyclic)	57	NaNH₂	C₆H₆	25
C₃						
	n-C₃H₇I	n-C₃H₇C(C₆H₅)₂CN	88	KOC₄H₉-t	Xylene-t-C₄H₉OH	27
	i-C₃H₇I	i-C₃H₇C(C₆H₅)₂CN	72	KOC₄H₉-t	Xylene	27
	CH₂=CHCH₂Cl	CH₂=CHCH₂C(C₆H₅)₂CN	94	NaNH₂	C₆H₆	25, 329
	CH₂=CHCH₂Br	CH₂=CHCH₂C(C₆H₅)₂CN	72	KOC₄H₉-t	Xylene-t-C₄H₉OH	27
	CH₃CHClCH₂Br	CH₃CHClCH₂C(C₆H₅)₂CN	47	NaNH₂	C₆H₆	25
	Br(CH₂)₃Br	Br(CH₂)₃C(C₆H₅)₂CN	—	NaNH₂	C₆H₆	1057
	H₃CCH——CH₂ \O/	CH₂——C(C₆H₅)₂ / H₃CCH C=NH \O/	57	KOC₄H₉-t	t-C₄H₉OH	27
	H₃CCH——CH₂ \O/	CH₂——C(C₆H₅)₂ / H₃CCH C=NH \O/	80	NaNH₂	C₆H₆	329

Note: References 577–1080 are on pp. 322–331.

† The methylating agent was not specified.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
	C_6H_5 (*Cont.*)	$H_3CCH\!-\!CH_2$ (O)	$CH_2\!-\!C(C_6H_5)_2$ / H_3CCH / CO / O	69	$NaNH_2$	C_6H_6	25
		$CH_2\!=\!CBrCH_2Br$	$CH_2\!=\!CBrCH_2C(C_6H_5)_2CN$	71	$NaNH_2$	C_6H_6	25
		C_4					
		$(CH_3)_2N(CH_2)_2Cl$	$(CH_3)_2N(CH_2)_2C(C_6H_5)_2CN$	70	$NaNH_2$	C_6H_6	1057, 26
		$(CH_3)_2N(CH_2)_2Cl$	$(CH_3)_2N(CH_2)_2C(C_6H_5)_2CN$	92	$NaNH_2$	Toluene	1023
		$BrCH_2CO_2C_2H_5$	$C_2H_5O_2CCH_2C(C_6H_5)_2CN$	90	$NaOC_2H_5$	Ethanol	1058
		$Br(CH_2)_4Br$	$Br(CH_2)_4C(C_6H_5)_2CN$	30	$NaNH_2$	C_6H_6	1057
C_6H_5		C_5	$\{(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ / $(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$	ca. 46	$KOC_4H_9\text{-}t$	Xylene-t-C_4H_9OH	27
		$(CH_3)_2NCH_2CH(CH_3)Cl$	$\{(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ / $(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$	ca. 46	$NaNH_2$	C_6H_6	27, 26, 91
		$(CH_3)_2NCH_2CH(CH_3)Cl$	$\{(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ / $(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$	ca. 39			
		$(CH_3)_2NCH_2CH(CH_3)Cl$	$\{(CH_3)_2NCH(CH_3)CH_2\text{-}C(C_6H_5)_2CN$ / $(CH_3)_2NCH_2CH(CH_3)\text{-}C(C_6H_5)_2CN$	36	$NaNH_2$	C_6H_6	25
		$(CH_3)_2NCH(CH_3)CH_2Cl$	$NC(CH_2)_2CH(CH_3)\text{-}C(C_6H_5)_2CN$	—			
		$CH_3CHCl(CH_2)_2CN$	(C_6H_5) / CN / NH / H_3C (cyclopentane)	Low	$NaNH_2$	C_6H_6	1059
				0			

Halide	Product	Yield (%)	Condensing agent	Solvent	References
ClCH₂CH(CH₃)CH₂CN	NCCH₂CH(CH₃)CH₂-C(C₆H₅)₂CN	—	NaNH₂	C₆H₆	1059
Br(CH₂)₂CO₂C₂H₅	C₂H₅O₂C(CH₂)₂C(C₆H₅)₂CN	ca. 75	NaNH₂	C₆H₆	1053
C₆					
(C₂H₅O)₂CHCH₂Cl	(C₂H₅O)₂CHCH₂C(C₆H₅)₂CN	—	NaNH₂	C₆H₆	1060
(C₂H₅)₂N(CH₂)₂Cl	(C₂H₅)₂N(CH₂)₂C(C₆H₅)₂CN	70-87	NaNH₂	C₆H₆	1057
β-(1-Pyrrolidyl)ethyl chloride hydrochloride	α,α-Diphenyl-γ-(1-pyrrolidyl)-butyronitrile	84	NaNH₂	C₆H₆	1057,191
β-(4-Morpholinyl)ethyl chloride	α,α-Diphenyl-γ-(4-morpholinyl)-butyronitrile	56	NaNH₂	C₆H₆	1057
β-(1-Piperidyl)ethyl chloride	α,α-Diphenyl-γ-(1-piperidyl)-butyronitrile	73	NaNH₂	C₆H₆	91, 93, 1057
C₇					
(C₂H₅)₂N(CH₂)₂Cl	(C₂H₅)₂N(CH₂)₂C(C₆H₅)₂CN	75	NaNH₂	C₆H₆	1057
(C₂H₅)₂NCH₂CH(CH₃)Cl	(C₂H₅)₂NCH₂CH(CH₃)-C(C₆H₅)₂CN and (C₂H₅)₂NCH(CH₃)CH₂-C(C₆H₅)₂CN	—	NaNH₂	C₆H₆	1061
C₆H₅CH₂Cl	C₆H₅CH₂C(C₆H₅)₂CN	83	NaOC₂H₅	Ethanol	564
C₆H₅CH₂Cl	C₆H₅CH₂C(C₆H₅)₂CN	—	NaNH₂	Ether	61
C₆H₅CH₂Cl	C₆H₅CH₂C(C₆H₅)₂CN	99	KNH₂	Liquid NH₃-ether	195
β-(2-Methyl-1-pyrrolidyl)ethyl chloride	α,α-Diphenyl-γ-(2-methyl-1-pyrrolidyl)butyronitrile	73	NaNH₂	C₆H₆	191
β-(1-Piperidyl)ethyl chloride	α,α-Diphenyl-γ-(1-piperidyl)-butyronitrile	—	NaNH₂	C₆H₆	26
1-(4-Morpholinyl)-2-chloropropane	{ α,α-Diphenyl-γ-(4-morpholinyl)-valeronitrile α,α-Diphenyl-γ-(4-morpholinyl)-i-valeronitrile	48 32	NaNH₂	C₆H₆	25, 91
2-(4-Morpholinyl)propyl chloride	{ α,α-Diphenyl-γ-(4-morpholinyl)-valeronitrile α,α-Diphenyl-γ-(4-morpholinyl)-i-valeronitrile	30 20	NaNH₂	C₆H₆	25

Note: References 577–1080 are on pp. 322–331.

TABLE XIV—*Continued*

ALKYLATION OF MONONITRILES, RCH(R')CN

R	R'	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
C₆H₅	C₆H₅ (*Cont.*)	C_8					
		$C_6H_5CH(CH_3)Cl$	$C_6H_5CH(CH_3)C(C_6H_5)_2CN$	80	KNH₂	Liquid NH₃-ether	195
				64	NaNH₂	C_6H_6	1001
		γ-(1-Piperidyl)propyl chloride	α,α-Diphenyl-δ-(1-piperidyl)-valeronitrile				
		1-(1'-Piperidyl)-2-chloropropane	α,α-Diphenyl-γ-(1-piperidyl)-valeronitrile and α,α-Diphenyl-γ-(1-piperidyl)-i-valeronitrile	—	NaNH₂	C_6H_6	91, 1061, 1062
		C_9					
		$C_6H_5N(CH_3)(CH_2)_2Cl$	$C_6H_5N(CH_3)(CH_2)_2C(C_6H_5)_2CN$	77	NaNH₂	C_6H_6	1063
		C_{10}					
		$(n\text{-}C_4H_9)_2N(CH_2)_2Cl$	$(n\text{-}C_4H_9)_2N(CH_2)_2C(C_6H_5)_2CN$	06	NaNH₂	C_6H_6	1057
		$C_6H_5CH_2N(CH_3)(CH_2)_2Cl$ CH₃	$C_6H_5CH_2N(CH_3)(CH_2)_2\text{-}C(C_6H_5)_2CN$	81	NaNH₂	C_6H_6	1093
		C_{11}					
		$C_6H_5CH_2N(CH_3)\text{-}CH_2CH(CH_3)Cl$	{ $C_6H_5CH_2N(CH_3)CH_2\text{-}CH(CH_3)C(C_6H_5)_2CN$	16	NaNH₂	C_6H_6	1063
			$C_6H_5CH_2N(CH_3)CH(CH_3)\text{-}CH_2C(C_6H_5)_2CN$	23			

TABLE XV

ALKYLATION OF ALKYLIDENEACETONITRILES

Compound Alkylated	Alkylating Agent	Product	Yield, %	Base	Solvent	Reference
Cyclopentylidene-(2-thienyl)-acetonitrile	(CH₃)₂N(CH₂)₂Cl	α-(1-Cyclopentenyl)-α-(2-thienyl)-acetonitrile γ-(dimethylamino)butyronitrile	—	NaNH₂	C₆H₆	193
	β-(1-Piperidyl)ethyl chloride	α-(1-Cyclopentenyl)-α-(2-thienyl)-butyronitrile γ-(1-piperidyl)butyronitrile	—	NaNH₂	C₆H₆	193
Cyclopentylidene(phenyl)-acetonitrile	(CH₃)₂N(CH₂)₂Cl	α-(1-Cyclopentenyl)-α-phenyl-butyronitrile γ-(dimethylamino)butyronitrile	65	NaNH₂	C₆H₆	193
	β-(1-Piperidyl)ethyl chloride	α-(1-Cyclopentenyl)-α-phenyl-butyronitrile γ-(1-piperidyl)butyronitrile	—	NaNH₂	C₆H₆	193
Cyclopentylidene-(p-methoxy-phenyl)acetonitrile	(CH₃)₂N(CH₂)₂Cl	α-(1-Cyclopentenyl)-α-(p-methoxy-phenyl)-γ-(dimethylamino)-butyronitrile	—	NaNH₂	C₆H₆	193
Cyclohexylidene(phenyl)-acetonitrile	n-C₃H₇I	n-Propyl-(1-cyclohexenyl)phenyl-acetonitrile	82	NaNH₂	C₆H₆	171
	CH₂=CHCH₂Br	Allyl-(1-cyclohexenyl)phenyl-acetonitrile	77	NaNH₂	Ether	171
	n-C₄H₉I	None	—	NaOC₂H₅	Ethanol	259
	β-(1-Piperidyl)ethyl chloride	α-(1-Cyclohexenyl)-α-phenyl-butyronitrile γ-(1-piperidyl)butyronitrile	92	NaNH₂	Toluene	192

TABLE XVI

REDUCTIONS LEADING TO ALKYLMALONIC ESTERS OR ACIDS

Compound Reduced	Reducing Agent	Product	Yield, %	Reference
CH₂=C(CO₂C₂H₅)₂	H₂—Ni	CH₃CH(CO₂C₂H₅)₂	95	1065
CH₃CH=C(CO₂C₂H₅)₂	AlHg₂	C₂H₅CH(CO₂C₂H₅)₂	—	1066
	H₂—Pd/C	C₂H₅CH(CO₂C₂H₅)₂	90	340
	H₄—PdCl₂	C₂H₅CH(CO₂C₂H₅)₂	—	346
	H₂—Ni	C₂H₅CH(CO₂C₂H₅)₂	93	1065

Substance	Catalyst	Product	Yield (%)	References
$C_2H_5CH{=}C(CO_2C_2H_5)_2$	H_2—Pd/C	$n\text{-}C_3H_7CH(CO_2C_2H_5)_2$	90	340
$(CH_3)_2C{=}C(CO_2C_2H_5)_2$	H_2—Ni	$i\text{-}C_3H_7CH(CO_2C_2H_5)_2$	96	340, 1068
$n\text{-}C_3H_7CH{=}C(CO_2C_2H_5)_2$	H_2—Pd/C	$n\text{-}C_4H_9CH(CO_2C_2H_5)_2$	93–96	340
	H_2—Ni	$n\text{-}C_4H_9CH(CO_2C_2H_5)_2$	95	1065
$C_2H_5C(CH_3){=}C(CO_2C_2H_5)_2$	H_2*	$C_2H_5CH(CH_3)CH(CO_2C_2H_5)_2$	95–100	1067
$CH_3CH(CH_3)CH{=}C(CO_2C_2H_5)_2$	H_2—Pd/C	$n\text{-}C_5H_{11}CH(CO_2C_2H_5)_2$	79	277
$i\text{-}C_3H_7CH{=}C(CO_2C_2H_5)_2$	H_2—Pd/C	$i\text{-}C_5H_{11}CH(CO_2C_2H_5)_2$	96–97	340
Diethyl cyclopentylidenemalonate	H_2*	Diethyl cyclopentylmalonate	95–100	1067
Diethyl 2-cyclopentenylmalonate	H_2—PtO$_2$	Diethyl cyclopentylmalonate	99	927
Furfurylidenemalonic acid	NaHg$_x$	Furfurylmalonic acid	—	355
Diethyl furfurylidenemalonate	H_2—Ni	Diethyl furfurylmalonate	96	1069, 1065
2-Thenylidenemalonic acid	NaHg$_x$	2-Thenylmalonic acid	85	358
Diethyl (2-pyrrylmethylene)malonate	H_2—PtO$_2$	Diethyl (2-pyrrolidylmethyl)malonate	95	1070
$CH_2{=}CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	H_2—Ni	$n\text{-}C_3H_7C(NHCOCH_3)(CO_2C_2H_5)_2$	—	232
$CH_3CH{=}CHCH_2C(NHCOCH_3)(CO_2C_2H_5)_2$	H_2—Ni	$n\text{-}C_4H_9C(NHCOCH_3)(CO_2C_2H_5)_2$	—	442
$n\text{-}C_7H_{15}CH{=}C(CO_2C_2H_5)_2$	H_2—Ni	$n\text{-}C_7H_{15}CH(CO_2C_2H_5)_2$	97	1065
$C_6H_5CH{=}C(CO_2H)_2$	NaHg$_x$	$C_6H_5CH_2CH(CO_2H)_2$	—	354
$C_6H_5CH{=}C(CO_2C_2H_5)_2$	AlHg$_x$	$C_6H_5CH_2CH(CO_2C_2H_5)_2$	60	350, 343
	H_2—Ni	$C_6H_5CH_2CH(CO_2C_2H_5)_2$	97	1065
$p\text{-}CH_3OC_6H_4CH{=}C(CO_2C_2H_5)_2$	H_2—Ni	$p\text{-}CH_3OC_6H_4CH_2CH(CO_2C_2H_5)_2$	100	950, 360, 1071
Diethyl (2,5-dimethoxybenzylidene)-malonate	H_2*	Diethyl (2,5-dimethoxybenzyl)malonate	—	1072
(2,3,4-Trimethylbenzylidene)malonic acid	H_2—Pd	(2,3,4-Trimethylbenzyl)malonic acid	—	361
Diethyl di(2-cyclopentenyl)malonate	H_2—Ni	Diethyl di(cyclopentyl)malonate	—	925
Dimethyl phenyl-(2-cyclohexenyl)malonate	H_2—PtO$_2$	Dimethyl phenyl(cyclohexoxyl)malonate	90	534
Diethyl allyl-(β-naphthyl)malonate	H_2—Pd/C	Diethyl n-propyl-(β-naphthyl)malonate	82	952
Diethyl allyl-(9-phenanthryl)malonate	H_2—Pd/C	Diethyl n-propyl-(9-phenanthryl)malonate	98	955

Note: References 577–1080 are on pp. 322–331.

* The catalyst employed was not stated.

TABLE XVII

REDUCTION OF THE ALKYLIDENE AND ARYLIDENE DERIVATIVES OF CYANOACETIC ACID, CYANOACETIC ESTERS, AND MALONONITRILE

Compound Reduced	Reducing Agent	Product	Yield, %	Reference
CH₃CHO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	C₂H₅CH(CN)CO₂C₂H₅	80–85	363
C₂H₅CHO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	n-C₃H₇CH(CN)CO₂C₂H₅	94	363
(CH₃)₂C·C(CN)CO₂C₂H₅	AlHg₂	i-C₃H₇CH(CN)CO₂C₂H₅	63	351
(CH₃)₂C=C(CN)CO₂C₂H₅	H₂—Pd/C	i-C₃H₇CH(CN)CO₂C₂H₅	90–93	363
(CH₃)₂CO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	n-C₄H₉CH(CN)CO₂C₂H₅	94–96	1073, 363
n-C₃H₇CHO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	C₂H₅CH(CH₃)CH(CN)CO₂C₂H₅	90	340
C₂H₅C(CH₃)=C(CN)CO₂C₂H₅	H₂—Pd/C	C₂H₅CH(CH₃)CH(CN)CO₂C₂H₅	98	363
i-C₃H₇CHO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	i-C₄H₉CH(CN)CO₂C₂H₅	66	364
CH₃CH(OH)CH₂CHO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	n-C₃H₇CH(CN)CO₂C₂H₅	67	277
n-C₃H₇C(CH₃)=C(CN)₂	H₂—Pd/C	n-C₃H₇CH(CH₃)CH(CN)₂	90–97	340, 363
n-C₃H₇C(CH₃)=C(CN)CO₂C₂H₅	H₂—Pd/C	n-C₃H₇CH(CH₃)CH(CN)CO₂C₂H₅	95	363
i-C₃H₇CHO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	i-C₅H₁₁CH(CN)CO₂C₂H₅	79	351
Ethyl cyclopentylidenecyanoacetate	AlHg₂	Ethyl cyclopentylcyanoacetate	41–63	363
i-C₃H₇COCH₃ + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	Ethyl (1,3-dimethylbutyl)cyanoacetate	84	575
(CH₃)₂C=CHC(CH₃)=C(CN)CO₂CH₃	H₂—Pd/C	i-C₄H₉CH(CH₃)CH(CN)CO₂CH₃	92	340
Ethyl cyclohexoxylidenecyanoacetate	H₂—Pd/C	Ethyl cyclohexoxylcyanoacetate	84	351
Ethyl cyclohexylidenecyanoacetate	AlHg₂	Ethyl cyclohexylcyanoacetate	91–98	363
Cyclohexanone + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	Ethyl cyclohexylcyanoacetate	71	363
n-C₄H₉CHO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	Ethyl n-heptylcyanoacetate	71	363
n-C₅H₁₁COCH₃ + CH₂(CN)CO₂C₂H₅	H₂—Pd/SrCO₃	Ethyl (1-methylhexyl)cyanoacetate	—	317
n-C₅H₁₁C(CH₃)=C(CN)CO₂C₂H₅	H₂—Pd/C	Ethyl (1-methylhexyl)cyanoacetate	39	363
(n-C₃H₇)₂CO + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	Ethyl [1-(n-propyl)butyl]cyanoacetate	73–81	363
n-C₄H₉COCH₃ + CH₂(CN)CO₂C₂H₅	H₂—Pd/C	Ethyl (1-methylheptyl)cyanoacetate		363

Ethyl 2-methylcyclohexylidenecyano-acetate	AlHg$_x$	Ethyl (2-methylcyclohexyl)cyanoacetate	—	363
Ethyl 3-methylcyclohexylidenecyano-acetate	AlHg$_x$	Ethyl (3-methylcyclohexyl)cyanoacetate	83	352
Ethyl 4-methylcyclohexylidenecyano-acetate	AlHg$_x$	Ethyl (4-methylcyclohexyl)cyanoacetate	87	352
C$_6$H$_5$CH=C(CN)CO$_2$H	NaHg$_x$	C$_6$H$_5$CH$_2$CH(CN)CO$_2$H	ca. 85	357
C$_6$H$_5$CH=C(CN)CO$_2$C$_2$H$_5$	NaHg$_x$	C$_6$H$_5$CH$_2$CH(CN)CO$_2$C$_2$H$_5$	86	993
C$_6$H$_5$CHO + CH$_2$(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	C$_6$H$_5$CH$_2$CH(CN)CO$_2$C$_2$H$_5$	63	363, 364
o-HOC$_6$H$_4$CH=C(CN)CO$_2$H	NaHg$_x$	o-HOC$_6$H$_4$CH$_2$CH(CN)CO$_2$H	ca. 85	357
m-HOC$_6$H$_4$CH=C(CN)CO$_2$H	NaHg$_x$	m-HOC$_6$H$_4$CH$_2$CH(CN)CO$_2$H	ca. 85	357
2,4-Dihydroxybenzylidenecyanoacetic acid	NaHg$_x$	(2,4-Dihydroxybenzyl)cyanoacetic acid	ca. 85	357
Ethyl cycloheptylidenecyanoacetate	AlHg$_x$	Ethyl cycloheptylcyanoacetate	72	351
p-CH$_3$OC$_6$H$_4$CH=C(CN)CO$_2$H	NaHg$_x$	p-Methoxybenzylcyanoacetic acid	ca. 85	357
Piperonylidenecyanoacetic acid	NaHg$_x$	(3,4-Methylenedioxybenzyl)cyanoacetic acid	ca. 85	357
C$_6$H$_5$CH$_2$C(CH$_3$)=C(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	C$_6$H$_5$CH$_2$CH(CH$_3$)CH(CN)CO$_2$C$_2$H$_5$	94	340
Ethyl 1-indanylidenecyanoacetate	H$_2$—Pd/C	Ethyl 1-indanylcyanoacetate	51	217
(C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_3$CHO + CH$_2$(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	(C$_2$H$_5$O$_2$C)$_2$CH(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$	39	362
(C$_2$H$_5$O$_2$C)$_2$C(C$_2$H$_5$)(CH$_2$)$_3$CHO + CH$_2$(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	(C$_2$H$_5$O$_2$C)$_2$C(C$_2$H$_5$)(CH$_2$)$_3$CH(CN)CO$_2$C$_2$H$_5$	85	362
(C$_2$H$_5$O$_2$C)$_2$C(OCOCH$_3$)(CH$_2$)$_3$CHO + CH$_2$(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	(C$_2$H$_5$O$_2$C)$_2$C(OCOCH$_3$)(CH$_2$)$_3$-CH(CN)CO$_2$C$_2$H$_5$	35	362
(C$_2$H$_5$O$_2$C)$_2$C(NHCOCH$_3$)(CH$_2$)$_3$CHO + CH$_2$(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	(C$_2$H$_5$O$_2$C)$_2$C(NHCOCH$_3$)(CH$_2$)$_3$-CH(CN)CO$_2$C$_2$H$_5$	27	362
o-C$_6$H$_5$C$_6$H$_4$CH$_2$CH=C(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	o-C$_6$H$_5$C$_6$H$_4$CH$_2$CH(CN)CO$_2$C$_2$H$_5$	60	340
(C$_2$H$_5$O$_2$C)$_2$C(C$_{10}$H$_{21}$-n)(CH$_2$)$_3$CHO + CH$_2$(CN)CO$_2$C$_2$H$_5$	H$_2$—Pd/C	(C$_2$H$_5$O$_2$C)$_2$C(C$_{10}$H$_{21}$-n)(CH$_2$)$_3$-CH(CN)CO$_2$C$_2$H$_5$	32	362

Note: References 577–1080 are on pp. 322–331.

TABLE XVIII

Addition of Grignard Reagents to Alkylidenemalonic Esters

Alkylidene Ester	Grignard Reagent	Product	Yield, %	Reference
$(CH_3)_2C=C(CO_2C_2H_5)_2$	CH_3MgI	$(CH_3)_3CCH(CO_2C_2H_5)_2$	37	157
	$n\text{-}C_3H_7MgBr$	$n\text{-}C_3H_7C(CH_3)_2CH(CO_2C_2H_5)_2$	31	157
	$n\text{-}C_4H_9MgBr$	$\begin{cases} n\text{-}C_4H_9C(CH_3)_2CH(CO_2C_2H_5)_2 \\ (CH_3)_2CHCH(CO_2C_2H_5)_2 \end{cases}$	40 / 20	367 / 367
	C_6H_5MgBr	$C_6H_5C(CH_3)_2CH(CO_2C_2H_5)_2$	40	367
	$C_6H_5CH_2MgCl$	$C_6H_5CH_2C(CH_3)_2CH(CO_2C_2H_5)_2$	80	367
$C_6H_5CH=C(CO_2C_2H_5)_2$	CH_3MgI	$C_6H_5CH(CH_3)CH(CO_2C_2H_5)_2$	—	954
	C_6H_5MgBr	$(C_6H_5)_2CHCH(CO_2C_2H_5)_2$	92	954, 156
	$o\text{-}CH_3C_6H_4MgBr$	$o\text{-}CH_3C_6H_4CH(C_6H_5)CH_2CO_2H$	—	1074
	$p\text{-}CH_3C_6H_4MgBr$	$p\text{-}CH_3C_6H_4CH(C_6H_5)CH(CO_2C_2H_5)_2$	23	829
	$p\text{-}CH_3OC_6H_4MgBr$	$p\text{-}CH_3OC_6H_4CH(C_6H_4)CH(CO_2C_2H_5)_2$	—	829
	α-Naphthylmagnesium bromide	$\alpha\text{-}C_{10}H_7CH(C_6H_5)CH(CO_2C_2H_5)_2$	74	829
	C_6H_5MgBr	$o\text{-}CH_3OC_6H_4CH(C_6H_5)CH(CO_2C_2H_5)_2$	—	1074
	$p\text{-}CH_3C_6H_4MgBr$	$(p\text{-}CH_3C_6H_4)_2CHCHCH(CO_2C_2H_5)_2$	90	150
	$p\text{-}CH_3OC_6H_4MgBr$	$(p\text{-}CH_3OC_6H_4)_2CHCH(CO_2C_2H_5)_2$	32	829

Note: References 577–1080 are on pp. 322–331.
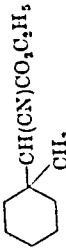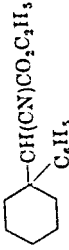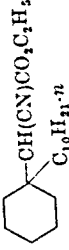
TABLE XIX

Addition of Grignard Reagents to Alkylidenecyanoacetic Acids and to Alkylidenemalononitriles

Alkylidene Derivative	Grignard Reagent	Product	Yield, %	Reference
$(CH_3)_2C=C(CN)CO_2H$	$n\text{-}C_3H_7MgBr$	$n\text{-}C_3H_7C(CH_3)_2CH_2CN$	41	367
	C_6H_5MgBr	$C_6H_5C(CH_3)_2CH_2CN$	80	367
	$C_6H_5CH_2MgCl$	$C_6H_5CH_2C(CH_3)_2CH_2CN$	68	367
$(CH_3)_2C=C(CN)CO_2K$	$n\text{-}C_3H_7MgBr$	$n\text{-}C_3H_7C(CH_3)_2CH_2CN$	17	367
	C_6H_5MgBr	$C_6H_5C(CH_3)_2CH_2CN$	30	367

Substrate	Grignard Reagent	Product	Yield (%)	References
$(CH_3)_2C{=}C(CN)CO_2C_2H_5$	$C_6H_5CH_2MgCl$	$C_6H_5CH_2C(CH_3)_2CH_2CN$	33	367
	CH_3I	$(CH_3)_3CCH(CN)CO_2C_2H_5$	75	159
	$n\text{-}C_3H_7MgBr$	$n\text{-}C_3H_7C(CH_3)_2CH(CN)CO_2C_2H_5$	42	159
	$n\text{-}C_4H_9MgBr$	$n\text{-}C_4H_9C(CH_3)_2CH(CN)CO_2C_2H_5$	40	367
		$\{(CH_3)_2CHCH(CN)CO_2C_2H_5$	15	367, 159
	C_6H_5MgBr	$C_6H_5C(CH_3)_2CH(CN)CO_2C_2H_5$	63	367, 159
	$C_6H_5CH_2MgCl$	$C_6H_5CH_2C(CH_3)_2CH(CN)CO_2C_2H_5$	85	367
	$C_6H_5CH_2MgBr$	$C_6H_5CH_2C(CH_3)_2CH(CN)CO_2C_2H_5$	49	159
$C_2H_5C(CH_3){=}C(CN)CO_2C_2H_5$	CH_3I	$C_2H_5C(CH_3)_2CH(CN)CO_2C_2H_5$	41	159
	$n\text{-}C_3H_7MgBr$	$n\text{-}C_3H_7C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	27–44	368, 1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	31–44	
	$i\text{-}C_3H_7MgBr$	$i\text{-}C_3H_7C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	39	1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	20	
	$n\text{-}C_4H_9MgBr$	$n\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	12–73	368, 1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	19–32	
	$i\text{-}C_4H_9MgBr$	$i\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	31	368, 1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	51	
	$sec\text{-}C_4H_9MgBr$	$\{sec\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	8	1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	40	
	$t\text{-}C_4H_9MgCl$	$\{t\text{-}C_4H_9C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	3	1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	63	
	$n\text{-}C_5H_{11}MgBr$	$\{n\text{-}C_5H_{11}C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	49	1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	22	
	$n\text{-}C_6H_{13}MgBr$	$\{n\text{-}C_6H_{13}C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	45	1075
		$C_2H_5CH(CH_3)CH(CN)CO_2C_2H_5$	24	
	C_6H_5MgBr	$C_6H_5C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	79	367
	$p\text{-}ClC_6H_4MgBr$	$p\text{-}ClC_6H_4C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	73	367
	$C_6H_5CH_2MgCl$	$C_6H_5CH_2C(C_2H_5)(CH_3)CH(CN)CO_2C_2H_5$	88	367
	$n\text{-}C_4H_9MgBr$	$n\text{-}C_4H_9C(CH_3)_2CH(CN)_2$	35	367
		$\{(CH_3)_2CHCH(CN)_2$	19	
$(CH_3)_2C{=}C(CN)_2$	C_6H_5MgBr	$C_6H_5C(CH_3)_2CH(CN)_2$	6	367
	$C_6H_5CH_2MgCl$	$C_6H_5CH_2C(CH_3)_2CH(CN)_2$	76	367

TABLE XIX—Continued

ADDITION OF GRIGNARD REAGENTS TO ALKYLIDENECYANOACETIC ACIDS AND ESTERS AND TO ALKYLIDENEMALONONITRILES

Compound Arylated	Reagent	Product	Yield, %	Reference
Ethyl cyclohexylidene-cyanoacetate	CH_3MgI	[cyclohexane ring] $CH(CN)CO_2C_2H_5$ / CH_3	45	1076
	C_6H_5MgBr	[cyclohexane ring] $CH(CN)CO_2C_2H_5$ / C_6H_5	44	1077
	$n\text{-}C_{10}H_{21}MgBr$	[cyclohexane ring] $CH(CN)CO_2C_2H_5$ / $C_{10}H_{21}\text{-}n$	14	1076
$C_6H_5CH{=}C(CN)CO_2C_2H_5$	CH_3MgI	$C_6H_5CH(CH_3)CH(CN)CO_2C_2H_5$	—	994
	$i\text{-}C_3H_7MgBr$	$C_6H_5CH(C_3H_7\text{-}i)CH(CN)CO_2C_2H_5$	—	994
	C_6H_5MgBr	$(C_6H_5)_2CHCH(CN)CO_2C_2H_5$	—	994
	$C_6H_5C{\equiv}CMgBr$	$C_6H_5C{\equiv}CCH(C_6H_5)CH(CN)CO_2C_2H_5$	—	994
	α-Naphthylmagnesium bromide	$\alpha\text{-}C_{10}H_7CH(C_6H_5)CH(CN)CO_2C_2H_5$	—	994
[cyclohexane ring] $={C(CN)CO_2C_2H_5}$	C_6H_5MgBr	[cyclohexane ring] C_6H_5 / $CH(CN)CO_2C_2H_5$ / $CO_2C_2H_5$	14	1077

Note References 577–1080 are on pp. 322–331.

TABLE XX

ARYLATION OF DERIVATIVES OF MESOXALIC AND TARTRONIC ACIDS

Compound Arylated	Arylating Agent	Product	Yield, %	Catalyst	Solvent	Reference
$OC(CO_2C_2H_5)_2$	C_6H_6	$(C_6H_5)_2C(CO_2C_2H_5)_2$	33	H_2SO_4	C_6H_6	278, 180, 1078
	C_6H_5OH	$(p\text{-}HOC_6H_4)_2C(CO_2C_2H_5)_2$	—	HCl	None	278

Reactant	Reagent	Product	Yield (%)	Catalyst	Solvent	References
	$CH_3C_6H_5$	$(p\text{-}CH_3C_6H_4)_2C(CO_2C_2H_5)_2$	—	H_2SO_4	Toluene	1079, 278, 1078
	$CH_3OC_6H_5$	$(p\text{-}CH_3OC_6H_4)_2C(CO_2C_2H_5)_2$	—	H_2SO_4	Anisole	1080
$OC(CO_2CH_3)_2$	$CH_3OC_6H_5$	$(p\text{-}CH_3OC_6H_4)_2C(CO_2C_2H_5)_2$	—	$SnCl_4$	Anisole	371
$OC(CO_2C_2H_5)_2$	$CH_3OC_6H_5$	$(p\text{-}CH_3OC_6H_4)_2C(CO_2CH_3)_2$	—	H_2SO_4	Anisole	1080
	$o\text{-}CH_3C_6H_4OH$	Diethyl di-(4-hydroxy-3-methylphenyl)malonate	66	HCl	None	278
	$p\text{-}CH_3C_6H_4CH_3$	Diethyl (2,5-dimethylphenyl)tartronato	51–57	$SnCl_4$	p-Xylene	370
$OC(CO_2CH_3)_2$	$o\text{-}CH_3C_6H_4CH_3$	Diethyl di-(3,4-dimethylphenyl)malonate	—	H_2SO_4	c-Xylene	1079
	$o\text{-}CH_3C_6H_4CH_3$	Dimethyl di-(3,4-dimethylphenyl)malonate	—	H_2SO_4	o-Xylene	1079
$OC(CO_2C_2H_5)_2$	$C_2H_5OC_6H_5$	Dimethyl di-(p-ethoxyphenyl)malonate	—	H_2SO_4	Phenetole	1080
	$C_2H_5OC_6H_5$	Diethyl di-(p-ethoxyphenyl)malonate	—	H_2SO_4	Phenetole	1080
	α-Naphthylmagnesium bromide	$\alpha\text{-}C_{10}H_7C(OCOC_6H_5)(CO_2C_2H_5)_2$	—	—	Ether-toluene	372
	9-Phenanthryl-magnesium bromide	$9\text{-}C_{14}H_9C(OH)(CO_2C_2H_5)_2$	46	—	Ether-toluene	372
$C_6H_5C(OH)(CO_2C_2H_5)_2$	$CH_3C_6H_5$	$p\text{-}CH_3C_6H_4C(C_6H_5)(CO_2C_2H_5)_2$	—	H_2SO_4	Toluene	1079
$p\text{-}CH_3C_6H_4\text{-}C(OH)(CO_2C_2H_5)_2$	C_6H_6	$p\text{-}CH_3C_6H_4C(C_6H_5)(CO_2C_2H_5)_2$	—	H_2SO_4	C_6H_6	1079
$p\text{-}(CH_3)_2NC_6H_4\text{-}C(OH)(CO_2C_2H_5)_2$	$C_6H_5N(CH_3)_2$	$[p\text{-}(CH_3)_2NC_6H_4]_2C(CO_2C_2H_5)_2$	80	$POCl_3$	$C_6H_5N(CH_3)_2$	373
$p\text{-}(C_2H_5)_2NC_6H_4\text{-}C(OH)(CO_2C_2H_5)_2$	$C_6H_5N(C_2H_5)_2$	$p\text{-}(C_2H_5)_2NC_6H_4\text{-}C[(C_6H_4N(CH_3)_2\text{-}p)](CO_2C_2H_5)_2$	—	$POCl_3$	$C_6H_5N(C_2H_5)_2$	373
$p\text{-}(C_2H_5)_2NC_6H_4\text{-}C(OH)(CO_2CH_3)_2$	$C_6H_5N(CH_3)_2$	$[p\text{-}(CH_3)_2NC_6H_4]_2C(CO_2CH_3)_2$	—	$POCl_3$	$C_6H_5N(CH_3)_2$	373
$p\text{-}(C_2H_5)_2NC_6H_4\text{-}C(OH)(CO_2C_2H_5)_2$	$C_6H_5N(C_2H_5)_2$	$p\text{-}(C_2H_5)_2NC_6H_4\text{-}C[(C_6H_4N(CH_3)_2\text{-}p)](CO_2CH_3)_2$	—	$POCl_3$	$C_6H_5N(C_2H_5)_2$	373
	$C_6H_5N(C_2H_5)_2$	$[p\text{-}(C_2H_5)_2NC_6H_4]_2C(CO_2C_2H_5)_2$	—	$POCl_3$	$C_6H_5N(C_2H_5)_2$	373

Note: References 577–1080 are on pp. 322–331.

REFERENCES TO TABLES I-XX

577 Conrad and Bischoff, *Ann.*, **204**, 143 (1880).

578 Bischoff and Rach, *Ann.*, **234**, 54 (1886).

579 Meyer and Bock, *Ann.*, **347**, 93 (1906).

580 Züblin, *Ber.*, **12**, 1112 (1879).

581 Funk, *Ber.*, **26**, 2568 (1893).

582 Olivier, *Rec. trav. chim.*, **55**, 1027 (1936).

583 Crawford, *J. Am. Chem. Soc.*, **56**, 139 (1934).

584 Conrad and Guthzeit, *Ber.*, **15**, 2841 (1882).

585 Guthzeit and Dressel, *Ber.*, **22**, 1413 (1889).

586 Urushibara, *Bull. Chem. Soc. Japan*, **2**, 26 (1927).

587 Coutelle, *J. prakt. Chem.*, [2] **73**, 49 (1906).

588 Zelinsky and Doroschewsky, *Ber.*, **27**, 3374 (1894).

589 Dimroth, *Ber.*, **35**, 2881 (1902).

590 Ingold and Powell, *J. Chem. Soc.*, **119**, 1222 (1921).

591 Hunter, *Chem. News*, **131**, 131 (1925).

592 Conrad, *Ann.*, **204**, 127 (1880).

593 Gault and Salomon, *Ann. chim. Paris*, [10] **2**, 133 (1924).

594 Conrad, *Ber.*, **12**, 749 (1879).

595 Schey, *Rec. trav. chim.*, **16**, 356 (1897).

596 Meunier, *Compt. rend.*, **137**, 714 (1903).

597 Daimler, *Ann.*, **249**, 173 (1888).

598 Michael, *Am. Chem. J.*, **25**, 419 (1901).

599 Joukowsky, *J. prakt. Chem.*, [2] **39**, 446 (1889).

600 Lean and Lees, *J. Chem. Soc.*, **71**, 1062 (1897).

601 Röder, *Ann.*, **227**, 13 (1885).

602 Noyes and Kyriakides, *J. Am. Chem. Soc.*, **32**, 1057 (1910).

603 Perkin, *Ber.*, **19**, 2038 (1886).

604 Perkin, *Ber.*, **17**, 54 (1884).

605 Infiesta, Martin, Guzmán, and Alberola, *Anales real soc. españ. fis. y quim. Madrid*, **47B**, 453 (1951) [*C. A.*, **46**, 3953 (1952).]

606 Bennett, *J. Chem. Soc.*, **127**, 1277 (1925).

607 Leuchs and Gieseler, *Ber.*, **45**, 2114 (1912).

608 Ruhemann, *Ber.*, **29**, 1016 (1896).

609 Kleber, *Ann.*, **246**, 97 (1888).

610 Rericha and Protiva, *Chem. Listy*, **44**, 232 (1950) [*C. A.*, **45**, 8017 (1951)].

611 Backer and Toxopéus, *Rec. trav. chim.*, **45**, 895 (1926).

612 Mishin and Polochanskaya, *Colloid J.* (*U.S.S.R.*), **2**, 317 (1936) [*C. A.*, **30**, 6261 (1936)].

613 Stiassny, *Monatsh. Chem.*, **12**, 589 (1891).

614 Fürth, *Monatsh. Chem.*, **9**, 308 (1888).

615 Conrad and Bischoff, *Ber.*, **13**, 595 (1880).

616 Linstead and Rydon, *J. Chem. Soc.*, **1933**, 580.

617 Shonle, U.S. pat. 1,842,293 [*C. A.*, **26**, 1617 (1932)].

618 Böeseken and Mass Geesteranus, *Rec. trav. chim.*, **51**, 551 (1932).

619 Conrad and Bischoff, *Ann.*, **204**, 166 (1880).

620 Matweeff, *J. prakt. Chem.*, [2] **39**, 451 (1889).

621 Hill and Fischer, *J. Am. Chem. Soc.*, **44**, 2582 (1922).

622 Favorskaya and Yakovlev, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **22**, 122 (1952) [*C. A.*, **46**, 11119 (1952)].

623 Fischer and Bergmann, *Ann.*, **398**, 96 (1913).

624 Venus-Danilova, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **8**, 477 (1938) [*C. A.*, **32**, 7897 (1938)].

625 Mariella and Raube, *Bol. col. quim. Puerto Rico*, **8**, 24 (1951) [*C. A.*, **46**, 4491 (1952)].

626 Marburg, *Ber.*, **28**, 8 (1895).

[627] Willstätter and Ettlinger, *Ann.*, **326**, 91 (1903).

[628] Willstätter, *Ber.*, **33**, 1160 (1900).

[629] Dutta, *Science and Culture India*, **5**, 560 (1940) [*C. A.*, **34**, 6933 (1940)].

[630] Baeyer, *Ann.*, **278**, 88 (1893).

[631] Perkin, *Ber.*, **18**, 3246 (1885).

[632] Curtius and Grandel, *J. prakt. Chem.*, [2] **94**, 339 (1917).

[633] Perkin, *Ber.*, **16**, 1787 (1883).

[634] Gault and Salomon, *Compt. rend.*, **174**, 754 (1922).

[635] Bischoff, *Ber.*, **29**, 966 (1896).

[636] Hudlický, *Chem. Listy*, **40**, 125 (1946) [*C. A.*, **45**, 560 (1951)].

[637] Bua and Tibaldi, *Farm. sci. e tec. Pavia*, **6**, 448 (1951) [*C. A.*, **46**, 8004 (1952)].

[638] Perkin and Simonsen, *J. Chem. Soc.*, **91**, 840 (1907).

[639] Perkin and Simonsen, *J. Chem. Soc.*, **91**, 816 (1907).

[640] Adams and Marvel, *J. Am. Chem. Soc.*, **42**, 310 (1920).

[641] Armendt and Adams, *J. Am. Chem. Soc.*, **52**, 1289 (1930).

[642] Bentley and Perkin, *J. Chem. Soc.*, **73**, 45 (1898).

[643] Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **A19**, No. 28, 9 (1945) [*C. A.*, **41**, 1604 (1947)].

[644] Chichibabin and Katznelson, *Bull. acad. sci., U.R.S.S., Classe sci. math. nat.*, **1933**, 267 [*C. A.*, **27**, 3698 (1933)].

[645] Katznelson and Kondakova, *Compt. rend. acad. sci. U.R.S.S.* [*N.S.*], **2**, 21 (1934) [*C. A.*, **28**, 5042 (1934)].

[646] Prelog and Božičović, *Ber.*, **72**, 1103 (1939).

[647] Linstead and Rydon, *J. Chem. Soc.*, **1934**, 1995.

[648] Eccott and Linstead, *J. Chem. Soc.*, **1929**, 2153.

[649] Arvin and Adams, *J. Am. Chem. Soc.*, **50**, 1983 (1928).

[650] Stauss, *Ber.*, **27**, 1228 (1894).

[651] Helferich and Speidel, *Ber.*, **54**, 2634 (1921).

[652] Tatevosyan and Tuteryan, *Bull. Acad. Sci. Armenian U.S.S.R.*, **1944**, No. 5, 29 [*C A.*, **40**, 3404 (1946)].

[653] Michael, *Ber.*, **38**, 3217 (1905).

[654] Paal, *Ber.*, **39**, 1436 (1906).

[655] Bischoff, *Ann.*, **214**, 38 (1882).

[656] Franke, Kroupa, Schweitzer, Winischofer, Klein-Lohr, Just, Hackl, Reyher, and Bader, *Monatsch. Chem.*, **69**, 167 (1936).

[657] Curtius, Sieber, Nadenheim, Hambsch, and Ritter, *J. prakt. Chem.*, [2] **125**, 152 (1930).

[658] Paal and Hoffmann, *Ber.*, **23**, 1495 (1890).

[659] Dewael and Weckering, *Bull. soc. chim. Belg.*, **33**, 495 (1924) [*C. A.*, **19**, 463 (1925)].

[660] Bergmann and Sprinzak, *Helv. Chim. Acta*, **20**, 590 (1937).

[661] Gaubert, Linstead, and Rydon, *J. Chem. Soc.*, **1937**, 1971.

[662] Schmid, *Helv. Chim. Acta*, **27**, 127 (1944).

[663] Allais and Mathieu, *Ann. pharm. franç.*, **9**, 275 (1951) [*C. A.*, **45**, 10499 (1951)].

[664] Behrens, Corse, Huff, Jones, Soper, and Whitehead, *J. Biol. Chem.*, **175**, 771 (1948).

[665] Colman and Perkin, *J. Chem. Soc.*, **53**, 185 (1888).

[666] Staudinger, Kreis, and Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).

[667] Ssolonina, *J. Russ. Phys. Chem. Soc.*, **33**, 734 (1902) (*Chem. Zentr.*, **1902**, I, 629).

[668] Karrer, Keller, and Usteri, *Helv. Chim. Acta*, **27**, 237 (1944).

[669] Bischoff, *Ann.*, **214**, 53 (1882).

[670] Emery, *Ber.*, **24**, 282 (1891).

[671] Alekseeva and Mezhov, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **22**, 1813 (1952) [*C. A.*, **47**, 5357 (1953)].

[672] Heinke and Perkin, *J. Chem. Soc.*, **69**, 1506 (1896).

[673] Conrad and Guthzeit, *Ber.*, **17**, 1185 (1884).

[674] Goldshmiedt and Knöpfer, *Monatsh. Chem.*, **17**, 506 (1896).

[675] Bischoff, *Ber.*, **29**, 1276 (1896).

[676] Verwey, *Ber.*, **29**, 1996 (1896).

[677] Ipatieff, Germain, and Pines, *Bull. soc. chim. France*, **1951**, 259.

[678] von Braun, Münch, and Deusser, *Ann.*, **465**, 52 (1928).

[679] Buu-Hoi and Cagniant, *Bull. soc. chim. France*, [5] **10**, 477 (1943).

[680] Arvin and Adams, *J. Am. Chem. Soc.*, **49**, 2940 (1927).

[681] Moffett, *Org. Syntheses*, **32**, 52 (1952).

[682] Barger, Robinson, and Smith, *J. Chem. Soc.*, **1937**, 718.

[683] Schudel and Rice, U.S. pat. 2,522,906 [*C. A.*, **45**, 6223 (1951)].

[684] Chargaff, *Ber.*, **65**, 745 (1932).

[685] Asano and Yamakawa, *J. Pharm. Soc. Japan*, **70**, 474 (1950) [*C. A.*, **45**, 5617 (1951)].

[686] Fieser, Berliner, Bondhus, Chang, Dauben, Ettlinger, Fawaz, Fields, Heidelberger, Heymann, Vaughan, Wilson, Wilson, Wu, Leffler, Hamlin, Matson, Moore, Moore, and Zaugg, *J. Am. Chem. Soc.*, **70**, 3174 (1948).

[687] Motti, *Anesthésie et analgésie*, **2**, 52 (1936) [*C. A.*, **31**, 3010 (1937)].

[688] Fourneau and Matti, *J. pharm. chim.*, [8] **14**, 513 (1931) [*C. A.*, **26**, 3073 (1932)].

[689] Strukov, *Zhur. Obshchel Khim.* (*J. Gen. Chem. U.S.S.R.*), **22**, 521 (1952) [*C. A.*, **47**, 2755 (1953)].

[690] Whitmore, Jones, and Noll, U.S. pat. 2,161,213 [*C. A.*, **33**, 7313 (1939)].

[691] Letsinger and Schnizer, *J. Org. Chem.*, **16**, 704 (1951).

[692] Howton and Davis, *J. Org. Chem.*, **16**, 1405 (1951).

[693] Stoll and Bolle, *Helv. Chim. Acta*, **21**, 1547 (1938).

[694] Pudovik and Arbuzov, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, **1947**, 501 [*C. A.*, **42**, 1887 (1948)].

[695] Newman and Wotiz, *J. Am. Chem. Soc.*, **71**, 1292 (1949).

[696] Freer and Perkin, *J. Chem. Soc.*, **53**, 202 (1888).

[697] Ipatiew, *J. Russ. Phys. Chem. Soc.*, **31**, 349 (1899) (*Chem. Zentr.*, **1899** II, 25).

[698] Cheney and Piening, *J. Am. Chem. Soc.*, **67**, 2213 (1945).

[699] Mannich and Margotte, *Ber.*, **68**, 273 (1935).

[700] Cason, Wallcave, and Whitside, *J. Org. Chem.*, **14**, 37 (1949).

[701] Barnstein, *Ann.*, **242**, 126 (1887).

[702] Leukart, *Ber.*, **18**, 2344 (1885).

[703] Buchner and Witter, *Ann.*, **284**, 225 (1895).

[704] Hiers and Adams, *J. Am. Chem. Soc.*, **48**, 2385 (1926).

[705] Ishiwata and Nozaki, *J. Pharm. Soc. Japan*, **71**, 1261 (1951) [*C. A.*, **46**, 5590 (1952)].

[706] Coffey, *Rec. trav. chim.*, **42**, 387 (1923).

[707] Kôtz and Hoffman, *J. prakt. Chem.*, [2] **110**, 101 (1925).

[708] Blicke, U.S. pat. 2,533,084 [*C. A.*, **45**, 3423 (1951)].

[709] Blicke, U.S. pat. 2,541,024 [*C. A.*, **46**, 537 (1952)].

[710] Koelsch, *J. Am. Chem. Soc.*, **66**, 1611 (1944.)

[711] Jackson and Soch, *Am. Chem. J.*, **18**, 133 (1896).

[712] Borsche, Stackmann, and Makaroff-Semljanski, *Ber.*, **49**, 2222 (1916).

[713] Sen and Bhargava, *J. Indian Chem. Soc.*, **25**, 538 (1948).

[714] Borsche and Trautner, *Ann.*, **447**, 1 (1926).

[715] Sen and Bhargava, *J. Indian Chem. Soc.*, **24**, 371 (1947).

[716] Prelog and Schönbaum, *Ann.*, **545**, 256 (1940).

[717] Ames, Bowman, and Mason, *J. Chem. Soc.*, **1950**, 174.

[718] Kondo and Suzuki, *Ber.*, **69**, 2459 (1936).

[719] Bondar and Zelinskiĭ, *Doklady Akad. Nauk S.S.S.R.*, **72**, 881 (1950) [*C. A.*, **44**, 9365 (1950)].

[720] Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 245 (1924).

[721] Huber, Clinton, Buck, Lawson, and Beal, *J. Am. Chem. Soc.*, **67**, 1148 (1945).

[722] Conrad and Bischoff, *Ann.*, **214**, 68 (1882).

[723] Conrad and Guthzeit, *Ber.*, **17**, 2285 (1884).

[724] Burschkies and Scholl, *Arch. Pharm.*, **281**, 328 (1943).

[725] Yohe and Adams, *J. Am. Chem. Soc.*, **50**, 1503 (1928).

[726] Burschkies and Scholl, *Chem. Ber.*, **82**, 224 (1949).

[727] Adams, Noller, and Arvin, U.S. pat. 1,678,175 [*C. A.*, **22**, 3491 (1928)].

728 Szarvasi, Dupont, and Dulou, *Chimie & industrie*, **62**, 143 (1949) [*C.A.*, **44**, 5345 (1950)].

729 Zelinsky and Alexandrow, *Ber.*, **34**, 3885 (1902).

730 Mousseron, Granger, and Winternitz, *Compt. rend.*, **217**, 246 (1943).

731 Haller and Barthe, *Ann. chim. Paris*, [6] **18**, 28 (1889).

732 Conrad, *Ann.*, **204**, 174 (1880).

733 Doebner and Kersten, *Ber.*, **38**, 2737 (1905).

734 Leuchs and Radulescu, *Ber.*, **45**, 189 (1912).

735 Gardner and Rydon, *J. Chem. Soc.*, **1938**, 42.

736 Barnes and Gordon, *J. Am. Chem. Soc.*, **71**, 2644 (1949).

737 Dankova, Bokova, Preobrazhenskiĭ, Petrushchenko, Il'shteĭn, and Stivetsov, *Zhur. Obshcheĭ Khim. (J. Gen. Chem. U.S.S.R.)*, **21**, 787 (1951) [*C. A.*, **45**, 9517 (1951)].

738 von Braun and Nelles, *Ber.*, **66**, 1464 (1933).

739 Leuchs and von Katinszky, *Ber.*, **55**, 710 (1922).

740 Lellmann and Schleich, *Ber.*, **20**, 434 (1887).

741 Reissert, *Ber.*, **27**, 2244 (1894).

742 Radulescu, *Bul. Soc. Stiinte Cluj*, **1**, 306 (1922) [*C. A.*, **18**, 1285 (1924)].

743 von Braun, Anton, and May, *Ber.*, **70**, 1250 (1937).

744 Clutterbuck, Raistrick, and Rintoul, *Trans. Roy. Soc.*, **B220**, 301 (1931).

745 Conrad and Bischoff, *Ann.*, **204**, 162 (1880).

746 Dickman, *Rev. fac. sci. univ. Istanbul*, **15A**, 108 (1950) [*C. A.*, **45**, 6154 (1951)].

747 Levene and Kuna, *J. Biol. Chem.*, **140**, 255 (1941).

748 Suzuki, *J. Pharm. Soc. Japan*, **56**, 860 (1936) [*C. A.*, **33**, 130 (1939)].

749 Weizmann, Bergmann, and Haskelberg, *Chemistry & Industry*, **15**, 587 (1937) [*C. A.*, **31**, 7407 (1937)].

750 Dutta, *J. Indian Chem. Soc.*, **19**, 79 (1942).

751 Matsui and Hirase, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **71**, 426 (1950) [*C. A.*, **45**, 8984 (1951)].

752 Bischoff, *Ber.*, **29**, 1504 (1896).

753 Bernton, Ing, and Perkin, *J. Chem. Soc.*, **125**, 1492 (1924).

754 Coleman, Callen, and Dornfeld, *J. Am. Chem. Soc.*, **68**, 1101 (1946).

755 Blicke and Centollela, *J. Am. Chem. Soc.*, **60**, 2923 (1938).

756 Rupe and Wolfsleben, *Ann.*, **395**, 111 (1913).

757 Leuchs and Reinhart, *Ber.*, **57**, 1208 (1924).

758 Bentley, Haworth, and Perkin, *J. Chem. Soc.*, **69**, 161 (1896).

759 Wessely and Wang, *Ber.*, **73**, 19 (1940).

760 Hoch, *Compt. rend.*, **192**, 1464 (1931).

761 Clemo and Swan, *J. Chem. Soc.*, **1949**, 487.

762 Curtius and Marangolo, *J. prakt. Chem.*, [2] **94**, 331 (1917).

763 Asano and Kawasaki, *J. Pharm. Soc. Japan*, **70**, 480 (1950) [*C. A.*, **45**, 5661 (1951)].

764 Chakravarti and Rao, *J. Chem. Soc.*, **1938**, 172.

765 Kues and Paal, *Ber.*, **18**, 3323 (1885).

766 Bischoff, *Ber.*, **16**, 1044 (1883).

767 von Baeyer and Perkin, *Ber.*, **17**, 122 (1884).

768 Leuchs and Sander, *Ber.*, **58**, 2200 (1925).

769 von Braun, Teuffert, and Manz, *Ber.*, **62**, 235 (1929).

770 Jones and Pyman, *J. Chem. Soc.*, **127**, 2588 (1925).

771 Przewalski, *J. Russ. Phys. Chem. Soc.*, **49**, 567 (1917) (*Chem. Zentr.*, **1923**, III, 664).

772 Günther, *Ber.*, **31**, 2134 (1898).

773 Gabriel, *Ber.*, **25**, 415 (1892).

774 Granger, *Ber.*, **28**, 1197 (1895).

775 Prelog, Heimbech, and Seiwerth, *Ber.*, **72**, 1319 (1939).

776 Merchant, Wickert, and Marvel, *J. Am. Chem. Soc.*, **49**, 1828 (1927).

777 Carter, *J. Am. Chem. Soc.*, **50**, 1967 (1928).

778 Wagner-Jauregg, Arnold, and Hüter, *Ber.*, **75**, 1293 (1942).

779 Kadesch, *J. Am. Chem. Soc.*, **66**, 1207 (1944).

780 Emerson and Heimsch, *J. Am. Chem. Soc.*, **72**, 5152 (1950).

781 Liebermann, *Ber.*, **32**, 260 (1899).

782 Cagniant, *Bull. soc. chim. France*, **1949**, 382.

783 Buu-Hoï and Cagniant, *Ber.*, **76**, 689 (1943).

784 Prout, Cason, and Ingersoll, *J. Am. Chem. Soc.*, **69**, 1233 (1947).

785 Forster and Cardwell, *J. Chem. Soc.*, **103**, 1338 (1913).

786 Mukherjee, *J. Indian Chem. Soc.*, **24**, 425 (1947).

787 Treibs and Mayer, *Chem. Ber.*, **85**, 612 (1952).

788 Ziegler and Weber, *Ann.*, **512**, 164 (1934).

789 Perkin and Robinson, *J. Chem. Soc.*, **119**, 1392 (1921).

790 Quadrat-i-Khuda and Mukherjee, *J. Indian Chem. Soc.*, **16**, 532 (1939).

791 Nenitzescu and Gavăt, *Ann.*, **519**, 260 (1935).

792 Marvel, MacCorquodale, Kendall, and Lazier, *J. Am. Chem. Soc.*, **46**, 2838 (1924).

793 Prelog, Šoštarič, and Guštak, *Ann.*, **545**, 247 (1940).

794 Kögl, Verbeek, Erxleben, and Borg, *Hoppe-Seyler's Z. physiol. Chem.*, **279**, 121 (1943).

795 Colonge and Pichat, *Bull. soc. chim. France*, **1949**, 177.

796 van der Zanden, de Vries, and Westerhof, *Rec. trav. chim.*, **62**, 383 (1943).

797 Smith and Agre, *J. Am. Chem. Soc.*, **60**, 652 (1938).

798 Guha and Bhattacharyya, *J. Indian Chem. Soc.*, **21**, 271 (1944).

799 Clemo, Groves, Munday, and Swan, *J. Chem. Soc.*, **1951**, 863.

800 Buchner and Dessauer, *Ber.*, **25**, 1153 (1892).

801 Hoffmann, *Ber.*, **34**, 1558 (1901).

802 Levene, West, Allen, and Van der Scheer, *J. Biol. Chem.*, **23**, 71 (1915).

803 Gaubert, Linstead, and Rydon, *J. Chem. Soc.*, **1937**, 1974.

804 Gensler, Behrmann, and Thomas, *J. Am. Chem. Soc.*, **73**, 1071 (1951).

805 Harmon and Marvel, *J. Am. Chem. Soc.*, **54**, 2515 (1932).

806 Tsatsas, *Ann. chim. Paris*, [12] **1**, 342 (1946).

807 Clemo, Haworth, and Walton, *J. Chem. Soc.*, **1929**, 2368.

808 Whittleston, *J. Am. Chem. Soc.*, **59**, 825 (1937).

809 Aitken, Badger, and Cook, *J. Chem. Soc.*, **1950**, 331.

810 Fuson, House, and Melby, *J. Am. Chem. Soc.*, **75**, 5952 (1953).

811 Gabriel, *Ber.*, **23**, 1767 (1890).

812 Kipping and Perkin, *J. Chem. Soc.*, **57**, 304 (1890).

813 Haerdi and Thorpe, *J. Chem. Soc.*, **127**, 1237 (1925).

814 Crossley and Perkin, *J. Chem. Soc.*, **65**, 987 (1894).

815 Lehman, Thompson, and Marvel, *J. Am. Chem. Soc.*, **55**, 1977 (1933).

816 Buckle, Pattison, and Saunders, *J. Chem. Soc.*, **1949**, 1471.

817 Tatevosyan and Babayan, *Zhur. Obshchei Khim. (J. Gen. Chem. U.S.S.R.)*, **22**, 1421 (1952) [*C. A.*, **47**, 4869 (1953)].

818 Fischer and Neber, *Ann.*, **496**, 1 (1932).

819 Bachmann, Gregg, and Pratt, *J. Am. Chem. Soc.*, **65**, 2314 (1943).

820 Ansell and Hey, *J. Chem. Soc.*, **1950**, 1683.

821 Buu-Hoï and Cagniant, *Rev. sci.*, **80**, 271 (1942) [*C. A.*, **39**, 3275 (1945)].

822 Billeter and Miescher, *Helv. Chim. Acta*, **29**, 859 (1946).

823 Lecocq and Buu-Hoï, *Compt. rend.*, **224**, 658 (1947).

824 Campbell, Corrigan, and Campbell, *J. Org. Chem.*, **16**, 1712 (1951).

825 Bachmann and Sheehan, *J. Am. Chem. Soc.*, **63**, 204 (1941).

826 Kalopissis and Gault, *Compt. rend.*, **231**, 1310 (1950).

827 Buu-Hoï and Cagniant, *Bull. soc. chim. France*, [5] **11**, 349 (1944).

828 Koelsch, *J. Am. Chem. Soc.*, **65**, 2460 (1943).

829 Holmberg, *Acta Acad. Aboensis Math. et Phys.*, **16**, 138 (1948) [*C. A.*, **45**, 558 (1951)].

830 von Braun and Manz, *Ann.*, **468**, 258 (1929).

831 Cohen, Cook, and Hewett, *J. Chem. Soc.*, **1936**, 52.

832 Smith and Lo, *J. Am. Chem. Soc.*, **70**, 2215 (1948).

833 Bachmann and Sheehan, *J. Am. Chem. Soc.*, **62**, 2687 (1940).

834 Wittig and Leo, *Ber.*, **62**, 1405 (1929).

835 Buu-Hoï and Cagniant, *Compt. rend.*, **214**, 493 (1942).

[836] Karrer, Favarger, Merz, and Milhaud, *Helv. Chim. Acta*, **31**, 1505 (1948).

[837] Dietrich and Lederer, *Compt. rend.*, **234**, 637 (1952).

[838] Short and Wang, *J. Chem. Soc.*, **1950**, 991.

[839] Wilds and Beck, *J. Am. Chem. Soc.*, **66**, 1688 (1944).

[840] Phillips and Mumford, *J. Chem. Soc.*, **1931**, 1732.

[841] Staudinger, Bier, and Lorentz, *Makromol. Chem.*, **3**, 251 (1949) [*C. A.*, **44**, 2443 (1950)].

[842] Guthzeit, *Ann.*, **206**, 351 (1881).

[843] van Loon and van der Linden, *Rec. trav. chim.*, **71**, 292 (1952).

[844] Toyama and Yamamoto, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **72**, 619 (1951) [*C. A.*, **47**, 1591 (1953)].

[845] Raphael and Sondheimer, *J. Chem. Soc.*, **1950**, 2100.

[846] Raphael and Sondheimer, *Nature*, **165**, 235 (1950).

[847] Stanley and Adams, *J. Am. Chem. Soc.*, **51**, 1515 (1929).

[848] Bachmann and Carmack, *J. Am. Chem. Soc.*, **63**, 2494 (1941).

[849] Fieser and Chamberlin, *J. Am. Chem. Soc.*, **70**, 71 (1948).

[850] Van Dyke and Adams, *J. Am. Chem. Soc.*, **48**, 2393 (1926).

[851] Henderson, *J. Chem. Soc.*, **51**, 224 (1887).

[852] Breitner, *Med. u. Chem. Abhandl. med. chem. Forschungsstätten I.G. Farbenind.*, **4**, 317 (1942) [*C. A.*, **38**, 4953 (1944)].

[853] Hale, Lycan, and Adams, *J. Am. Chem. Soc.*, **52**, 4536 (1930).

[854] Levene and Taylor, *J. Biol. Chem.*, **52**, 227 (1922).

[855] Polgar, Robinson, and Seijo, *J. Chem. Soc.*, **1949**, 1545.

[856] David, Polgar, and Robinson, *J. Chem. Soc.*, **1949**, 1541.

[857] Conrad and Guthzeit, *Ann.*, **214**, 76 (1882).

[858] Locquin and Cerchez, *Compt. rend.*, **186**, 1360 (1928).

[859] Cerchez, *Bull. soc. chim. France*, [4] **47**, 1381 (1930).

[860] J. Shapira and K. Dittmer, to be published.

[861] Koštíř and Král, *Chem. Listy*, **43**, 37 (1949) [*C. A.*, **45**, 562 (1951)].

[862] Capková-Jirků, Koštíř, and Vondráček, *Chem. Listy*, **44**, 114 (1950) [*C. A.*, **45**, 7962 (1951)].

[863] J. S. Meek and S. Minkowitz, to be published.

[864] J. S. Meek and J. W. Rowe, to be published.

[865] Vejdělek and Protiva, *Chem. Listy*, **45**, 44 (1951) [*C. A.*, **45**, 9011 (1951)].

[866] Goldsmith and Tishler, *J. Am. Chem. Soc.*, **68**, 144 (1946).

[867] Warner and Moe, Brit. pat. 658,413 [*C. A.*, **46**, 9588 (1952)].

[868] Rinderknecht and Niemann, *J. Am. Chem. Soc.*, **73**, 4259 (1951).

[869] Dittmer, Herz, and Chambers, *J. Biol. Chem.*, **166**, 541 (1946).

[870] Dittmer, Martin, Herz, and Cristol, *J. Am. Chem. Soc.*, **71**, 1201 (1949).

[871] Elks, Elliott, and Hems, *J. Chem. Soc.*, **1944**, 626.

[872] Auwers and Thorpe, *Ann.*, **285**, 310 (1895).

[873] Adams and Rogers, *J. Am. Chem. Soc.*, **63**, 228 (1941).

[874] Kitzing, *Ber.*, **27**, 1578 (1894).

[875] Kobayasi, *Ann.*, **536**, 143 (1938).

[876] Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **A23**, No. 15, 14 (1946) [*C. A.*, **41**, 5443 (1947)].

[877] Bischoff and Voit, *Ber.*, **23**, 639 (1890).

[878] Cagniant, *Compt. rend.*, **232**, 734 (1951).

[879] Cavanna and Ställberg-Stenhagen, *Atti accad. nazl. Lincei, Mem. Classe sci. fis. mat. e nat.*, [8] **3**, 31 (1950) [*C. A.*, **45**, 9470 (1951)].

[880] Noyes, *Ber.*, **33**, 54 (1900).

[881] Adkins and Davis, *J. Am. Chem. Soc.*, **71**, 2955 (1949).

[882] Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **26A**, No. 12, 28 (1948) [*C. A.*, **43**, 6160 (1949)].

[883] Ruzicka and Hosking, *Helv. Chim. Acta*, **13**, 1402 (1930).

[884] Robinson and Suginome, *J. Chem. Soc.*, **1932**, 304.

[885] Fieser and Novello, *J. Am. Chem. Soc.*, **62**, 1855 (1940).

886 Vargha and Gyorffy, *Magyar Chem. Folyóirat*, **50**, 6 (1944) [*C. A.*, **42**, 1219 (1948)].

887 Greer and Adams, *J. Am. Chem. Soc.*, **52**, 2540 (1930).

888 Stanley, Jay, and Adams, *J. Am. Chem. Soc.*, **51**, 1261 (1929).

889 Fernholz and Finkelstein, *J. Am. Chem. Soc.*, **60**, 2402 (1938).

890 Jones, U.S. pat. 2,363,003 [*C. A.*, **39**, 3791 (1945)].

891 Paal and Kühn, *Ber.*, **41**, 51 (1908).

892 Raper, *J. Chem. Soc.*, **91**, 1837 (1907).

893 Walter, U.S. pat. 2,354,231 [*C. A.*, **39**, 1416 (1945)].

894 Paal and Kühn, *Ber.*, **41**, 58 (1908).

895 Shonle, U.S. pat. 1,813,867 [*C. A.*, **25**, 5249 (1931)].

896 Huang-Minlon, *Contribs. Biol. Lab. Sci. Soc. China, Zool. Ser.*, **15**, 17 (1940) [*C. A.*, **36**, 80 (1942)].

897 Morren, Dony, and Levis, *J. pharm. Belg.*, **7**, 65 (1952) [*C. A.*, **47**, 5895 (1953)].

898 Bywater, U.S. pat. 2,200,538 [*C. A.*, **34**, 6019 (1940)].

899 Walter and Goodson, U.S. pat. 2,354,234. [*C. A.*, **39**, 1417 (1945)].

900 Plati, Strain, and Warren, *J. Am. Chem. Soc.*, **65**, 1273 (1943).

901 Hsueh and Marvel, *J. Am. Chem. Soc.*, **50**, 855 (1928).

902 Adams, Stanley, Ford, and Peterson, *J. Am. Chem. Soc.*, **49**, 2934 (1927).

903 Lévy, *Compt. rend.*, **202**, 1679 (1936).

904 Dittrich and Paal, *Ber.*, **21**, 3451 (1888).

905 Cocker, Cross, Fateen, Lipman, Stuart, Thompson, and Whyte, *J. Chem. Soc.*, **1950**, 1781.

906 Brunner and Wiedemann, *Monatsh. Chem.*, **66**, 438 (1935).

907 Meyer, *Compt. rend.*, **203**, 1074 (1936).

908 Meyer, *Compt. rend.*, **203**, 1370 (1936).

909 Kondakova and Katsnel'son, *Compt. rend. acad. sci.* (*U.R.S.S.*), **18**, 271 (1938) [*C. A.*, **32**, 4523 (1938)].

910 Work, *J. Chem. Soc.*, **1946**, 197.

911 Kolloff, Hunter, Woodruff, and Moffett, *J. Am. Chem. Soc.*, **70**, 3862 (1948).

912 Staudinger, Muntwyler, Ruzicka, and Seibt, *Helv. Chim. Acta*, **7**, 390 (1924).

913 Pratt and Archer, *J. Am. Chem. Soc.*, **70**, 4065 (1948).

914 Buu-Hoï and Cagniant, *Hoppe-Seyler's Z. physiol. Chem.*, **279**, 76 (1943).

915 Hildebrandt and Leube, Ger. pat. 494,320 [*C. A.*, **24**, 2756 (1930)].

916 Tatevosyan and Melikyan, *Zhur. Obshchei Khim.* (*J. Gen. Chem. U.S.S.R.*), **17**, 975 (1947) [*C. A.*, **42**, 1566 (1948)].

917 Tatevosyan and Nikogosyan, *Proc. Acad. Sci. Armenian S.S.R.*, **1945**, III, 15 [*C. A.*, **40**, 3397 (1946)].

918 Hall, Mahboob, and Turner, *J. Chem. Soc.*, **1952**, 1956.

919 von Braun and Kröper, *Ber.*, **62**, 2880 (1929).

920 Browning, Woodrow, and Adams, *J. Am. Chem. Soc.*, **52**, 1281 (1930).

921 Waltz, *Ann.*, **214**, 58 (1882).

922 Bischoff, *Ann.*, **214**, 61 (1882).

923 Bischoff and Mintz, *Ber.*, **23**, 653 (1890).

924 Leonard, *J. Am. Chem. Soc.*, **74**, 2915 (1952).

925 von Braun and Fischer, *Ber.*, **66**, 101 (1933).

926 von Braun and Kurtz, *Ber.*, **70**, 1224 (1937).

927 Moffett, Hart, and Hoehn, *J. Am. Chem. Soc.*, **69**, 1849 (1947).

928 Arvin and Adams, *J. Am. Chem. Soc.*, **50**, 1790 (1928).

929 Davies and Adams, *J. Am. Chem. Soc.*, **50**, 2297 (1928).

930 Leder-Pakkendorf, *Compt. rend. acad. sci.* (*U.R.S.S.*), **31**, 757 (1941) [*C. A.*, **37**, 871 (1943)].

931 McElvain and Laughton, *J. Am. Chem. Soc.*, **73**, 448 (1951).

932 Roberts and Selby, *J. Chem. Soc.*, **1951**, 2335.

933 Miescher and Hoffmann, *Helv. Chim. Acta*, **24**, 458 (1941).

934 Jackman, Bergman, and Archer, *J. Am. Chem. Soc.*, **70**, 497 (1948).

935 Buu-Hoï, Cagniant, and Mentzer, *Bull. soc. chim. France*, [5] **11**, 127 (1944).

[936] Charpentier, U.S. pat. 2,570,024 [*C. A.*, **46**, 3562 (1952)].

[937] Adams, Van Duuren, and Brown, *J. Am. Chem. Soc.*, **74**, 5608 (1952).

[938] Geissman and Tulagin, *J. Am. Chem. Soc.*, **66**, 719 (1944).

[939] Conrad and Bischoff, *Ann.*, **204**, 177 (1880).

[940] Simonsen, *J. Chem. Soc.*, **117**, 564 (1920).

[941] Ingold and Rogers, *J. Chem. Soc.*, **1935**, 717.

[942] Naik, Shah, and Nargund, *J. Univ. Bombay*, **19**, *Sect. A*, Pt. 3, *Sci. No. 28*, 19 (1950) [*C. A.*, **46**, 11124 (1952)].

[943] von Braun and Hamann, *Ber.*, **65**, 1580 (1932).

[944] Duff and Ingold, *J. Chem. Soc.*, **1934**, 87.

[945] von Braun, Manz, and Reinsch, *Ann.*, **468**, 277 (1929).

[946] Bergmann, *J. Org. Chem.*, **4**, 1 (1939).

[947] Ford and Adams, *J. Am. Chem. Soc.*, **52**, 1259 (1930).

[948] Tatevosyan and Vardanyan, *Proc. Acad. Sci. Armenian S.S.R.*, **4**, No. 3, 71 (1946) [*C. A.*, **41**, 432 (1947)].

[949] Buchta and Dauner, *Chem. Ber.*, **81**, 247 (1948).

[950] Jacques and Horeau, *Bull. soc. chim. France*, **1950**, 512.

[951] von Braun and Schattner, *Ber.*, **74**, 22 (1941).

[952] Cope, Meili and MacDowell, *J. Am. Chem. Soc.*, **78**, 2551 (1956).

[953] Bachmann and Anderson, *J. Org. Chem.*, **13**, 297 (1948).

[954] Kohler, *Am. Chem. J.*, **34**, 132 (1905).

[955] Cope, Field, MacDowell, and Wright, *J. Am. Chem. Soc.*, **78**, 2547 (1956).

[956] Kohler, *Am. Chem. J.*, **46**, 485 (1911).

[957] Staudinger and Kern, *Ber.*, **66**, 373 (1933).

[958] Kohler and Conant, *J. Am. Chem. Soc.*, **39**, 1699 (1917).

[959] Perkin, *J. Chem. Soc.*, **87**, 358 (1905).

[960] Gregory and Perkin, *J. Chem. Soc.*, **83**, 780 (1903).

[961] Kon, Linstead, and Maclennan, *J. Chem. Soc.*, **1932**, 2452.

[962] Henry, *Compt. rend.*, **104**, 1618 (1887).

[963] Henry, *Jahresber.*, **1889**, 637.

[964] Urushibara, *Bull. Chem. Soc. Japan*, **2**, 236 (1927).

[965] Errera, *Gazz. chim. ital.*, **27**, II, 393 (1897).

[966] Ruhemann and Browning, *J. Chem. Soc.*, **73**, 280 (1898).

[967] Errera, *Ber.*, **31**, 1241 (1898).

[968] Hadley, *J. Am. Chem. Soc.*, **34**, 923 (1912).

[969] Földi, Fodor, Demjén, Szekeres, and Halmos, *Ber.*, **75**, 755 (1942).

[970] Dai Nippon Celluloid Co., Jap. pat. 157,332 [*C. A.*, **43**, 9475 (1949)].

[971] Fischer and Brieger, *Ber.*, **48**, 1517 (1915).

[972] Fischer and Brieger, *Chem. Zentr.*, **86**, II, 222 (1915).

[973] Darapsky, *J. prakt. Chem.* [2], **146**, 250 (1936).

[974] Barthe, *Ann. chim. Paris*, [6] **27**, 239 (1892).

[975] Freylon, *Ann. chim. Paris*, [8] **19**, 562 (1910).

[976] I.G. Farbenindustrie, A.-G., Swiss pat. 116,292 [*Chem. Zentr.*, **97**, II, 2850 (1926)].

[977] Haller and Barthe, *Compt. rend.*, **106**, 1413 (1888).

[978] Curtius and Wirbatz, *J. prakt. Chem.*, [2] **125**, 267 (1930).

[979] Perkin, *J. Chem. Soc.*, **85**, 416 (1904).

[980] Wren and Haller, *J. Chem. Soc.*, **1937**, 230.

[981] Verkade and Hartman, *Rec. trav. chim.*, **52**, 945 (1933).

[982] Gagnon, Gaudry, and King, *J. Chem. Soc.*, **1944**, 13.

[973] Volwiler and Tabern, *J. Am. Chem. Soc.*, **58**, 1352 (1936).

[984] Bone and Sprankling, *J. Chem. Soc.*, **77**, 654 (1900).

[985] Bone and Sprankling, *J. Chem. Soc.*, **77**, 1298 (1900).

[986] Liebermann, *Ber.*, **32**, 916 (1899).

[987] Hellerman, *J. Am. Chem. Soc.*, **49**, 1735 (1927).

[988] Zelinsky, *Ber.*, **22**, 2823 (1889).

[989] Bone and Perkin, *J. Chem. Soc.*, **67**, 416 (1895).

[1043] Vasiliu, Dumitrascu, and Vulcan, *Soc. Chim. România Sect. Română Stiinte, Bul. Chim. Pura Apl.*, [2] **3A**, 54 (1941–1942) [*C. A.*, **38**, 5493 (1944).]

[1044] Panizzon, *Helv. Chim. Acta*, **27**, 1748 (1944) [*C. A.*, **40**, 3117 (1946)].

[1045] Vasiliu, *Bul. Soc. Chim. România*, **19A**, 75 (1937) [*C. A.*, **33**, 4207 (1939)].

[1046] Venus-Danilova and Bol'shukin, *Zhur. Obshchel. Khim. (J. Gen. Chem. U.S.S.R.)*, **7**, 2823 (1937) [*C. A.*, **32**, 2925 (1938)].

[1047] Upson and Thompson, *J. Am. Chem. Soc.*, **44**, 181 (1922).

[1048] Meyer, *Ber.*, **21**, 1306 (1888).

[1049] Walters and McElvain, *J. Am. Chem. Soc.*, **55**, 4625 (1933).

[1050] Bockmühl and Ehrhardt, Ger. pat. 473,329. [*Chem. Zentr.*, **100** (II), 218 (1929)].

[1051] Bockmühl and Schwarz, U.S. pat. 1,482,343. [*Chem. Zentr.*, **95** (II), 1631 (1924)].

[1052] Rising and Lowe, *J. Am. Chem. Soc.*, **52**, 2524 (1930).

[1053] Salmon-Legagneur and Neveu, *Compt. rend.*, **234**, 1060 (1952).

[1054] Vasiliu and Radvan, *Bul. Soc. Chim. România*, **20A**, 243 (1938) [*C. A.*, **34**, 4058 (1940)].

[1055] Blicke, U.S. pat. 2,542,466 [*C. A.*, **45**, 7141 (1951)].

[1056] Iwaya and Yoshida, *J. Pharm. Soc. Japan*, **71**, 1454 (1951) [*C. A.*, **46**, 7065 (1952)].

[1057] Dupré, Elks, Hems, Speyer, and Evans, *J. Chem. Soc.*, **1949**, 500.

[1058] Salmon-Legagneur, *Bull. soc. chim. France*, **1952**, 580.

[1059] Easton, Reiff, Svarnas, and Fish, *J. Am. Chem. Soc.*, **74**, 260 (1952).

[1060] Morrison and Rinderknecht, *J. Chem. Soc.*, **1950**, 1478.

[1061] Ofner and Walton, *J. Chem. Soc.*, **1950**, 2158.

[1062] Ofner, Thorp, and Walton, *Nature*, **163**, 479 (1949).

[1063] Wilson, *J. Chem. Soc.*, **1952**, 3524.

[1064] Löwenbein and Gagarin, *Ber.*, **58**, 2643 (1925).

[1065] Wojcik and Adkins, *J. Am. Chem. Soc.*, **56**, 2424 (1934).

[1066] Vogel, *J. Chem. Soc.*, **1927**, 1985.

[1067] Cope and Hardy, *J. Am. Chem. Soc.*, **62**, 3319 (1940).

[1068] Adkins and Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948).

[1069] Hinz, Meyer, and Schücking, *Ber.*, **76**, 676 (1943).

[1070] Clemo, Fletcher, Fulton, and Raper, *J. Chem. Soc.*, **1950**, 1140.

[1071] Horeau and Jacques, *Compt. rend.*, **228**, 1873 (1949).

[1072] Baltzly and Buck, *J. Am. Chem. Soc.*, **62**, 161 (1940).

[1073] Alexander and Cope, *Org. Syntheses*, **26**, 31 (1946).

[1074] Holmberg, *Acta Chem. Scand.*, **6**, 421 (1952) [*C. A.*, **47**, 2141 (1953)].

[1075] Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952).

[1076] Birch and Robinson, *J. Chem. Soc.*, **1943**, 501.

[1077] Barltrop and Nicholson, *J. Chem. Soc.*, **1951**, 2524.

[1078] Ando, *J. Chem. Soc. Japan*, **57**, 1351 (1936) [*C. A.*, **31**, 2596 (1937)].

[1079] Guyot and Esteva, *Compt. rend.*, **148**, 564 (1909).

[1080] Guyot and Esteva, *Compt. rend.*, **148**, 719 (1909).

CHAPTER 5

THE REACTION OF HALOGENS WITH SILVER SALTS OF CARBOXYLIC ACIDS

C. V. WILSON

Eastman Kodak Company

CONTENTS

INTRODUCTION

The action of halogens with *dry* metallic salts, particularly silver salts of carboxylic acids has merited earlier reviews.[1-2a] It has been pointed out that the halogen used, the ratio of silver salt to halogen, and the presence or absence of other active materials, such as olefins, acetylenes, or readily substituted aromatic rings play a large part in determining the

[1] Kleinberg, *Chem. Revs.*, **40**, 381 (1947).

[2] Staněk, *Chem. Listy*, **47**, 1244 (1953).

[2a] Johnson and Ingham, *Chem. Revs.*, **56**, 219 (1956).

course of the reactions. Thus, it is possible to produce (A) organic halides containing one less carbon atom than the original acid, RCO_2H; (B) esters, RCO_2R, derived from two molecules of the acid by loss of one molecule of carbon dioxide; (C) esters of 1,2-diols or of halohydrins; (D) halogenated aromatic compounds; and (E) halogenated acetylenes. These reactions may be represented by the following general equations.

(A) $$RCO_2Ag + X_2 \rightarrow RX + CO_2 + AgX$$

(B) $$2RCO_2Ag + X_2 \rightarrow RCO_2R + CO_2 + 2AgX$$

(AB) $$3RCO_2Ag + 2X_2 \rightarrow RCO_2R + RX + 2CO_2 + 3AgX$$

(C) $$RCO_2Ag + X_2 + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CHXR'' + AgX$$
$$2RCO_2Ag + X_2 + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CH(OCOR)R''$$
$$+ 2AgX$$

(D) $$RCO_2Ag + X_2 + ArH \rightarrow RCO_2H + ArX + AgX$$
$$ArCO_2Ag + X_2 \rightarrow X{-}Ar{-}CO_2H + AgX$$

(E) $$RCO_2Ag + X_2 + R'C{\equiv}CH \rightarrow R'C{\equiv}CX + RCO_2H + AgX$$
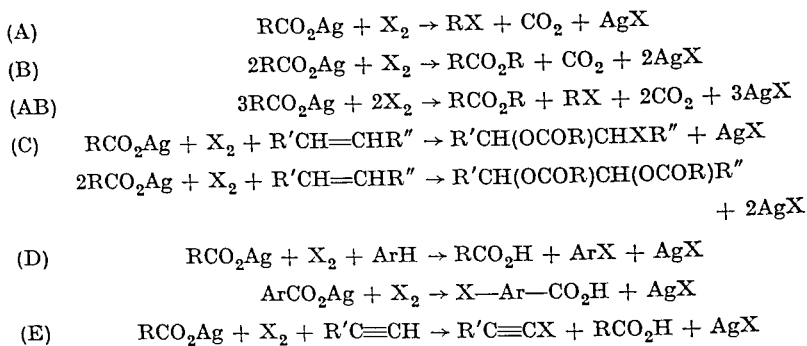
The reaction represented by A in which the molar silver salt-halogen ratio is 1 : 1, is due chiefly to Hunsdiecker;[3–5] it makes available a variety of compounds that are prepared only with difficulty by other procedures. Reaction B is generally known as the Simonini reaction;[6,7] it is carried out with a 2 : 1 molar ratio of silver salt to halogen (iodine only). Reaction AB, discovered by Oldham and Ubbelohde,[8] makes use of a 3 : 2 molar ratio of reactants. Reactions C and E are usually attributed to Prévost.[9–14] Reaction D proceeds only in the presence of a phenyl group (Ar) which undergoes electrophilic substitution readily,[15–18] or when R is of such a nature that the RCO_2^- ion is a very weak base, such as $CF_3CO_2^-$.[19]

[3] Hunsdiecker, Hunsdiecker, and Vogt, U.S. pat. 2,176,181 (1939) [C. A., 34, 1685 (1940)].
[4] Hunsdiecker and Hunsdiecker, Ber., 75, 291 (1942).
[5] Hunsdiecker, Hunsdiecker, and Vogt, Ger. pat. 730,410 (1942) [C. A., 38, 374 (1944)].
[6] Simonini, Monatsh., 13, 320 (1892).
[7] Simonini, Monatsh., 14, 81 (1893).
[8] Oldham and Ubbelohde, J. Chem. Soc., 1941, 368.
[9] Prévost, Compt. rend., 196, 1129 (1933).
[10] Prévost, Compt. rend., 197, 1661 (1933).
[11] Prévost and Lutz, Compt. rend., 198, 2264 (1934).
[12] Prévost, Compt. rend., 200, 942 (1935).
[13] Prévost and Wiemann, Compt. rend., 204, 700 (1937).
[14] Prévost and Wiemann, Compt. rend., 204, 989 (1937).
[15] Birnbaum and Reinherz, Ber., 15, 456 (1882).
[16] Barnes and Prochaska, J. Am. Chem. Soc., 72, 3188 (1950).
[17] Dauben and Tilles, J. Am. Chem. Soc., 72, 3185 (1950).
[18] Papa, Schwenk, and Klingsberg, J. Am. Chem. Soc., 72, 2623 (1950).
[19] Haszeldine and Sharp, J. Chem. Soc., 1952, 993.

NATURE OF THE REACTIONS

It is well established [20-22] that the primary product of the reaction between a dry silver salt of a carboxylic acid and halogen is an acyl hypohalite.

$$RCO_2Ag + X_2 \rightarrow RCO_2X + AgX$$

Thermal cleavage of this intermediate results in the formation of an alkyl halide with loss of carbon dioxide, and this is the basis of reaction A.

$$RCO_2X \rightarrow RX + CO_2$$
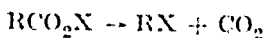
Extensive evidence favors a mechanism with the free radical $R\cdot$ as an intermediate in the conversion of RCO_2Br to RBr. First the reaction of optically active silver salts with bromine or of the intermediate acyl hypobromites I and II under a variety of conditions leads to totally racemized bromides III and IV.[23]   Although the alkyl bromide, if it had

$$C_2H_5CH(CH_3)CO_2Br \qquad\qquad n\text{-}C_3H_7CH(C_2H_5)CO_2Br$$
$$\text{I} \qquad\qquad\qquad\qquad\qquad \text{II}$$
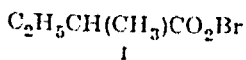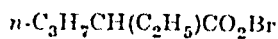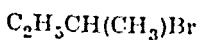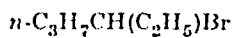
$$C_2H_5CH(CH_3)Br \qquad\qquad n\text{-}C_3H_7CH(C_2H_5)Br$$
$$\text{III} \qquad\qquad\qquad\qquad\qquad \text{IV}$$

been obtained optically active in these reactions, would have been racemized slowly by the silver bromide present, it was shown by control experiments that such racemization is too slow to account for most of the loss of optical activity observed during the reaction of the silver salt with bromine.   The reactions of optically active silver salts with bromine had previously been reported to yield optically inactive bromides,[24-26] but the significance of the results remained in doubt since it was not shown at that time that the loss in activity was not entirely due to racemization of the bromide by silver bromide.

It should be mentioned that silver (+)-α-phenylpropionate was reported to react with bromine in carbon tetrachloride to yield phenethyl bromide with 43% of the optical activity retained.[27]   It has been shown, however, that (+)-phenethyl bromide, when boiled with silver bromide in carbon tetrachloride under conditions of the reaction of the silver salt with bromine, is essentially completely racemized.[28,29]   This would

[20] Bockemüller and Hoffmann, *Ann.*, **519**, 165 (1935).

[21] Birckenbach, Goubeau, and Berninger, *Ber.*, **65**, 1339 (1932).

[22] Uschakov and Chistov, *Ber.*, **68**, 824 (1935).

[23] Winstein and Berr, Unpublished work; C. E. Berr, Ph.D. Thesis, University of California, Los Angeles, 1952; Winstein, *Bull soc. chim. France*, [5] **18**, 70c (1951).

[24] Arnold and Morgan, *J. Am. Chem. Soc.*, **70**, 4248 (1948).

[25] Heintzeler, *Ann.*, **569**, 102 (1950).

[26] Bell and Smyth, *J. Chem. Soc.*, **1949**, 2372.

[27] Arcus, Campbell and Kenyon, *Nature*, **163**, 287 (1949); *J. Chem. Soc.*, **1949**, 1510.

[28] Abbott and Arcus, *J. Chem. Soc.*, **1952**, 3195.

[29] Arcus and Boyd, *J. Chem. Soc.*, **1951**, 1580.

indicate that the substance responsible for the optical activity observed in the product of the silver salt reaction was not phenethyl bromide. This conclusion has been strengthened by the failure of several investigators[23,28,30] to isolate any phenethyl bromide from the reaction of silver α-phenylpropionate with bromine in carbon tetrachloride. A report[28] that silver (+)-2-ethylhexanoate with bromine gives (+)-3-bromoheptane requires further investigation.

That it is the intermediate R·, rather than R+ or R−,[31] which is responsible for the observed loss of activity during reaction has been supported by evidence from several sources. Thus, reactions that might have been expected to lead to the neopentyl carbonium ion invariably lead to products derived from its rearrangement product, the *t*-amyl carbonium ion.[32] Silver *t*-butylacetate, however, reacts with bromine to yield neopentyl bromide with no detectible amount of *t*-amyl bromide.[23,33] Similarly, reactions that might be expected to proceed by way of the cyclobutyl carbonium ion lead to mixtures of cyclobutyl, cyclopropylcarbinyl, and allylcarbinyl products.[34] The reaction of silver cyclobutanecarboxylate with bromine, however, yields cyclobutyl bromide accompanied by only a very small amount of rearranged products.[35]

While the neopentyl radical, $(CH_3)_3CCH_2·$, does not rearrange under conditions used to prepare it, the neophyl radical, $C_6H_5C(CH_3)_2CH_2·$, has been shown to rearrange in part to the more stable tertiary radical, $(CH_3)_2CCH_2C_6H_5$.[36] Examination of the reaction of the acyl hypobromite V has indicated that some of the tertiary bromide VI was formed by

$$C_6H_5C(CH_3)_2CH_2CO_2Br \qquad\qquad BrC(CH_3)_2CH_2C_6H_5$$
$$\text{V} \qquad\qquad\qquad\qquad\qquad \text{VI}$$
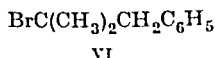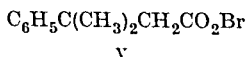
rearrangement in addition to the unrearranged product.[23] A control experiment showed that the unrearranged product, neophyl bromide, was stable toward the reaction conditions.

Additional evidence for the radical intermediate is provided by a study of the reaction of the silver salt of apocamphane-1-carboxylic acid.[37] Reactions proceeding by way of the apocamphyl carbonium ion have been

[30] Cason, Kalm, and Mills, *J. Org. Chem.*, **18**, 1670 (1953).

[31] Compare Rottenberg, *Experientia*, **7**, 432, (1951) [*C. A.*, **46**, 4336 (1952)].

[32] Ingold, *Structure and Mechanism in Organic Chemistry*, pp. 485–486, Cornell University Press, Ithaca, New York. 1953.

[33] Smith and Hull, *J. Am. Chem. Soc.*, **72**, 3309 (1950).

[34] Roberts and Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).

[35] Cason and Way, *J. Org. Chem.*, **14**, 32 (1949); Roberts and Chambers, *J. Am. Chem. Soc.*, **73**, 5039 (1951); Buchman and Conly, *ibid.*, **75**, 1990 (1953).

[36] Urry and Kharasch, *J. Am. Chem. Soc.*, **66**, 1438 (1944); Winstein and Seubold, *ibid.*, **69**, 2916 (1947); Urry and Nicolaides, *ibid.*, **74**, 5162 (1952).

[37] Wilder and Winston, *J. Am. Chem. Soc.*, **75**, 5370 (1953).

shown to be very much slower than their counterparts in acyclic systems.[38] On the other hand, there is no such retardation when the apocamphyl radical is involved.[39]   It was found, in fact, that silver apocamphane-1-carboxylate reacts readily with bromine in boiling petroleum ether to yield 1-bromoapocamphane in 50% yield, with no evidence of any retardation in rate by the bicyclic system.   The reaction in carbon tetrachloride was accompanied by the formation of a chlorine-containing by-product.[37]

Other observations which are suggestive of a free-radical chain mechanism are side-chain bromination of toluene,[19] the indication that there is an induction period when the reaction is carried out at low temperatures,[40] and an acceleration of the reaction by light.[20]

The most probable mechanism would appear to be the following.[41]

$$\text{Initiation } RCO_2Br \rightarrow RCO_2\cdot + Br\cdot$$

$$\text{Propagation } RCO_2\cdot \rightarrow R\cdot + CO_2$$

$$R\cdot + RCO_2Br \rightarrow RBr + RCO_2\cdot$$

$$\text{Termination } 2R\cdot \rightarrow R\text{---}R \text{ or } RH + \text{olefin}$$
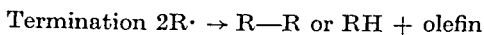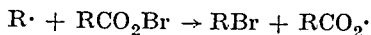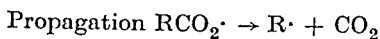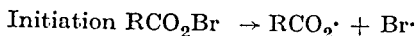
and/or

$$RCO_2\cdot + R\cdot \rightarrow RCO_2R$$
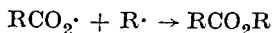
Another piece of evidence consistent with this picture is the following. The reaction of silver benzoate with bromine in carbon tetrachloride gives 53% of bromobenzene, 5% of chlorobenzene, and 6.7% of bromotrichloromethane. These products are readily explained if, superimposed on the sequence of reactions above, there is reaction of the phenyl radical with carbon tetrachloride as shown below.[16,17,*]

$$C_6H_5\cdot + ClCCl_3 \rightarrow C_6H_5Cl + \cdot CCl_3$$
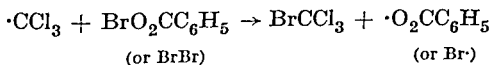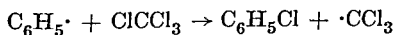
$$\cdot CCl_3 + BrO_2CC_6H_5 \rightarrow BrCCl_3 + \cdot O_2CC_6H_5$$
$$\text{(or BrBr)} \qquad\qquad\qquad \text{(or Br}\cdot\text{)}$$

[38] Bartlett and Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939).

[39] Kharasch, Engelmann, and Urry, *J. Am. Chem. Soc.*, **65**, 2428 (1943).

[40] Conly, *J. Am. Chem. Soc.*, **75**, 1148 (1953).

[41] Compare Price, *Mechanisms of Reactions at Carbon-Carbon Double Bonds*, p. 55, Interscience Publishers, New York, 1946.

* Wiberg and Shryne,[41a] on the basis of the report that silver (+)-2-ethylhexanoate with bromine gives (+)-3-bromoheptane,[28] suggested that the mechanism is a 1,3-intramolecular shift involving an electron-deficient group in the transition state—a mechanism first proposed by Rottenberg.[31]   Since the reported retention of optical activity in this reaction is in contradiction with the reports of racemization described on p. 335, caution must be exercised until confirmation is available.

[41a] Wiberg and Shryne, *J. Am. Chem. Soc.*, **77**, 2774 (1955).

When the silver salt of a carboxylic acid reacts with iodine in a $2:1$ molar ratio, the primarily formed acyl hypoiodite coordinates with the excess silver salt to form a complex.[6,7,42–17a] Many such complexes can be

$$2RCO_2Ag + I_2 \rightarrow RCO_2I + RCO_2Ag + AgI$$

$$RCO_2Ag + RCO_2I \rightarrow RCO_2Ag \cdot RCO_2I$$
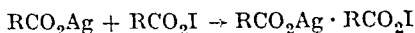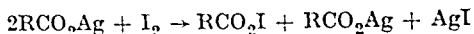
isolated. With others, however, the difference between the temperatures of formation and decomposition is too small to permit isolation. The thermal cleavage of the complex to give an ester is the basis of reaction B (Simonini reaction).

$$RCO_2Ag \cdot RCO_2I \rightarrow RCO_2R + CO_2 + AgI$$
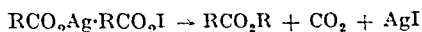
It is not clear what role, if any, the complex formation plays in the reaction, which appears to be composed of two parts. Available evidence suggests that the first stage, a reaction of the silver salt with iodine to give carbon dioxide and alkyl iodide, is closely related to the Hunsdiecker reaction discussed above. The second stage is an ionic reaction of the alkyl iodide thus formed with a second molecule of silver salt.[19] This

$$RCO_2Ag + I_2 \rightarrow RCO_2I + AgI$$

$$RCO_2I \rightarrow RI + CO_2$$

$$RI + RCO_2Ag \rightarrow RCO_2R + AgI$$
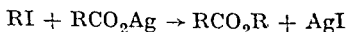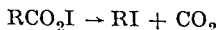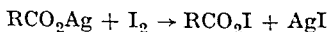
view is consistent with the fact that in the reaction of such substances as silver cyclobutanecarboxylate [44,48] a typical carbonium ion rearrangement occurs in the alcohol portion of the ester formed. The products are cyclobutyl, cyclopropylcarbinyl, and allylcarbinyl cyclobutanecarboxylates in yields of 32, 65, and 3%, respectively.

$$C_4H_7CO_2Ag + I_2 \rightarrow C_4H_7I + CO_2 + AgI$$

$$C_4H_7I + AgO_2CC_4H_7 \rightarrow C_4H_7O_2CC_4H_7 + C_3H_5CH_2O_2CC_4H_7$$

$$+ CH_2{=}CHCH_2CH_2O_2CC_4H_7$$
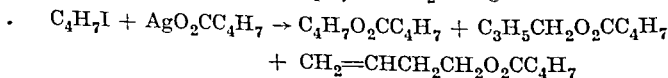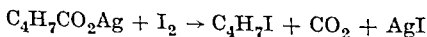
Failure to observe the formation of triphenylmethyl peroxide when silver triphenylacetate is treated with iodine in the presence of air has been interpreted as evidence that the triphenylmethyl radical is not an intermediate.[49] Such an argument is valid, however, only if it can be

[42] Heiduschka and Ripper, *Ber.*, **56**, 1736 (1923).

[43] Birnbaum and Gaier, *Ber.*, **13**, 1270 (1880).

[44] Demjanov and Dojarenko, *Ber.*, **40**, 2594 (1907).

[45] Gascard, *Compt. rend.*, **153**, 1484 (1911).

[46] Gascard, *Ann. chim.* (Paris), [9] **15**, 332 (1921).

[47] Panics, *Monatsh.*, **15**, 10 (1894).

[47a] Birnbaum, *Ann.*, **152**, 111 (1869).

[48] Roberts and Simons, *J. Am. Chem. Soc.*, **73**, 5487 (1951).

[49] Wieland and Fischer, *Ann.*, **446**, 49 (1925–26).

shown that the reaction of the triphenylmethyl radical with oxygen under the conditions employed is faster than its reaction with iodine.

While the Hunsdiecker and Simonini reactions produce halides and esters respectively, the reaction represented by AB gives rise to both of these products. The iodine triacyl postulated as an intermediate can be isolated when R is a long-chain alkyl group. Formed by the action of 2 moles of iodine on 3 moles of the silver salt as indicated below, such compounds decompose thermally to yield both alkyl halide and ester.[8]   In the

$$3RCO_2Ag + 2I_2 \rightarrow I(OCOR)_3 + 3AgI$$
$$I(OCOR)_3 \rightarrow RCO_2R + RI + 2CO_2$$
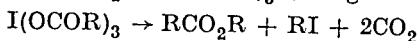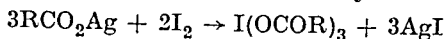
presence of excess iodine, the iodine triacyl decomposes to give a high yield of alkyl iodide.

$$I(OCOR)_3 + I_2 \rightarrow 3RI + 3CO_2$$
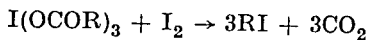
Water decomposes the triacyl to yield iodine and iodic acid.

$$I(OCOR)_3 + 3H_2O \rightarrow I(OH)_3 + 3RCO_2H$$
$$5I(OH)_3 \rightarrow 3HIO_3 + I_2 + 6H_2O$$
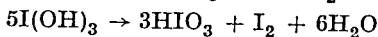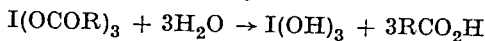
This, and the fact that triacyls such as iodine tris(trichloromethylacetate) conduct electricity with the iodine migrating toward the cathode, indicates the positive nature of the iodine in such materials.[50]

Nothing is known of the mechanism of these reactions. It seems likely, however, that they are radical chain reactions initiated by the dissociation of the iodine triacyl to acyl hypoiodite and acyloxy radicals.[8]   It is entirely reasonable that those acyloxy radicals that lose carbon dioxide

$$I(OCOR)_3 \rightarrow IOCOR + 2RCO_2\cdot$$
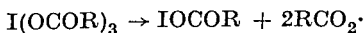
give alkyl radicals that react with iodine triacyl as shown below. A fuller

$$RCO_2\cdot \rightarrow R\cdot \xrightarrow{I(OCOR)_3} RCO_2R + IOCOR + RCO_2\cdot$$

understanding of the mechanism must await further investigation.

In the presence of ethylenic compounds the primarily formed acyl hypohalite adds to the double bond to form a haloester.

$$RCO_2X + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CHXR''$$
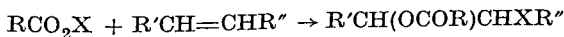
This is the basis of reaction C. The Simonini complex undergoes a similar reaction to yield first the ester of an iodohydrin and, finally, a diester. Presumably the complex dissociates, the acyl hypoiodite adds to the double bond, and the iodine is replaced by the molecule of silver salt formed by dissociation of the complex.[10]

$$RCO_2I\cdot RCO_2Ag \rightarrow RCO_2I + RCO_2Ag$$
$$RCO_2I + R'CH{=}CHR'' \rightarrow R'CH(OCOR)CHIR''$$
$$R'CH(OCOR)CHIR'' + RCO_2Ag \rightarrow R'CH(OCOR)CH(OCOR)R'' + AgI$$

[50] Fichter and Stern, *Helv. Chim. Acta*, **11**, 1256 (1928).
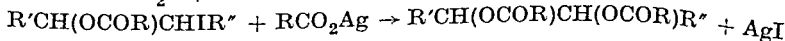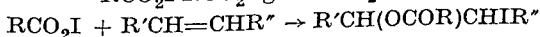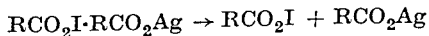
The products of the reaction suggest an ionic mechanism. Evidence that might be considered support for such a mechanism arises from the following fact: Silver (+) or (−)-2-ethylhexanoate when treated with bromine in carbon tetrachloride yields acyl hypohalites which add to styrene to give (+) or (−)-2-bromo-1-phenethyl-2-ethylhexanoate, which on hydrolysis with alkali yields (+) or (−)-2-ethylhexanoic acid in which a substantial percentage of the optical activity of the original acid is retained.[51] However, this reaction does not involve the asymmetric carbon atom and is not, therefore, diagnostic as to mechanism. The partial racemization presumably occurs during hydrolysis, for it has been shown that racemization of such esters can accompany hydrolysis.

Substitution of halogen in the benzene nucleus, as represented by reaction D, occurs most readily when R is the trifluoromethyl group.[19,52,53] However, if the aryl group is activated sufficiently to electrophilic attack, substitution may occur when R is methyl. The substituted products obtained are those expected through halogenation by an entity which carries a positive charge. Thus *ortho* and *para* substitution occur in compounds containing groups known to activate the aromatic nucleus to electrophilic attack, whereas substitution fails or occurs in the *meta* position when the substituent deactivates the nucleus. On this basis, the fission of the acyl hypohalite would be expected to proceed by an ionic mechanism. Thus, either the acyl hypohalite itself or X^+ formed by its dissociation can serve as the halogenating agent.

$$RCO_2X + C_6H_6 \rightarrow C_6H_5X + H^+ + RCO_2^-$$

or

$$RCO_2X \rightarrow RCO_2^- + X^+$$

$$X^+ + C_6H_6 \rightarrow C_6H_5X + H^+$$
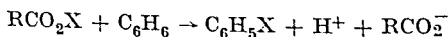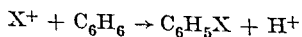
Fission by a free-radical mechanism would necessitate halogenation by halogen atoms. When an alkyl side chain is present, substitution of the side chain is the preferred reaction. However, the products of such a process have not been found in any of the reactions studied.

When the acyl hypohalite is derived from an ordinary alkyl or aryl carboxylic acid, it is a sufficiently poor halogenating agent in the absence of readily substituted aromatic rings to allow the free-radical dissociation followed by decarboxylation (Hunsdiecker reaction) to predominate. However, nuclear halogenation can be increased at the expense of the Hunsdiecker reaction either by adding a readily substituted aromatic compound such as veratrole[53a] or by using a more active acyl hypohalite

[51] Abbott and Arcus, *J. Chem. Soc.*, 1952, 1515.

[52] Henne and Zimmer, *J. Am. Chem. Soc.*, 73, 1362 (1951).

[53] Schwartz, *Anales soc. españ. fis. quim.*, 27, 683 (1929) [*C. A.*, 24, 589 (1930)].

[53a] Janssen, VanAllan, and Wilson, *J. Org. Chem.*, 20, 1326 (1955).

as the halogenating agent. Trifluoroacetyl hypobromite shows little tendency to undergo the Hunsdiecker decarboxylation at temperatures ordinarily employed with other acyl hypohalites. It is, therefore, particularly useful as a brominating agent.[19,52]

The other phase of reaction D involves the presence of readily substituted aromatic rings in the silver salt and thus in the acyl hypohalite. Again, either the hypohalite itself or X^+ formed by its dissociation acts as the halogenating agent.[17]
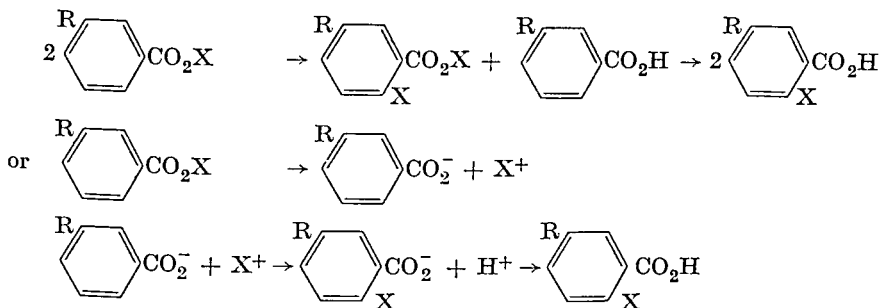
Substitution of halogen in acetylenes, as indicated by reaction E, probably occurs by a similar mechanism.

$$RCO_2X + R'C \equiv CH \rightarrow R'C \equiv CX + H^+ + RCO_2^-$$

or

$$RCO_2X \rightarrow RCO_2^- + X^+$$

$$X^+ + R'C \equiv CH \rightarrow R'C \equiv CX + H^+$$
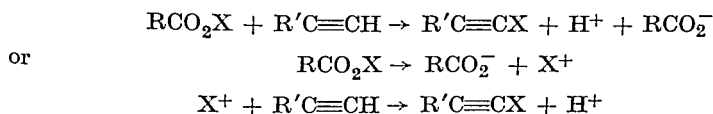
SCOPE AND LIMITATIONS OF THE REACTIONS

Thermal Cleavage of Acyl Hypohalites (Hunsdiecker Reaction)

The thermal decomposition of acyl hypohalites formed as intermediates in the halogen silver-salt reaction to produce compounds containing one carbon atom less than the original acid is perhaps the most important of the various silver salt-halogen reactions. The reaction is of general application in the aliphatic series, leading, with simple fatty acids of 2 to 18 carbon atoms, to excellent yields of alkyl halides.[3,20,25,30,54-58]

$$RCO_2Ag + X_2 \rightarrow RX + CO_2 + AgX$$
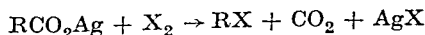
A substituent in the aliphatic chain in any position other than the

[54] Lüttringhaus and Schade, *Ber.*, **74**, 1565 (1941).
[55] Mehta, Mehta, and Thosar, *J. Indian Chem. Soc., Ind. Ed.*, **3**, 137 (1940).
[56] Borodine, *Ann.*, **119**, 121 (1861).
[57] Birnbaum, *Ann.*, **152**, 111 (1869).
[58] Cason and Winans, *J. Org. Chem.*, **15**, 142 (1950).

α-position does not interfere with the reaction unless it is itself capable of reaction with the acyl hypohalite. Thus, silver salts of alkyl-substituted fatty acids yield primary halides as do acids carrying a cycloalkyl substituent such as cyclopentylacetic acid.[5] Simple halogen derivatives, such as silver β-bromopropionate, yield dibromides.[40] Polyhalogen compounds have been obtained from silver salts of polyhalogen acids; thus, silver 9,10-dichloroöctadecanoate yields 1-bromo-8,9-dichloroheptadecane;[3] and 1,8,9,11,12-pentabromoheptadecane is obtained from silver 9,10,12,13-tetrabromoöctadecanoate.[59] When applied to acid esters, the reaction leads to ω-halo esters.[4,5,60-62] This is a useful reaction because ω-halo

$$RO_2C(CH_2)_nCO_2Ag + X_2 \rightarrow RO_2C(CH_2)_nX + CO_2 + AgX$$
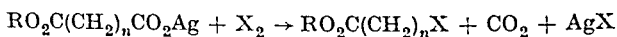
esters are not easily prepared by other procedures. Silver salts of acids in which there is an aryl substituent such as phenyl[25,63] or deactivated phenyl[16] also give primary halides. If, however, the substituent is a phenyl group readily substituted by electrophilic agents, there is halogenation of the ring and formation of a free acid without loss of carbon dioxide. For example, silver β-3-methoxyphenylpropionate when treated with bromine or iodine gives an excellent yield of β-2-bromo-(or iodo-)5-methoxyphenylpropionic acid.[18] Such complex substances as 3(α),12(β)-diacetoxynordesoxycholanic acid (VII) and 3 (α), 12(β)-diacetoxycholanic
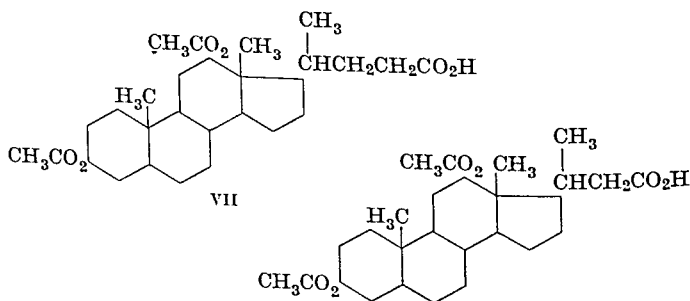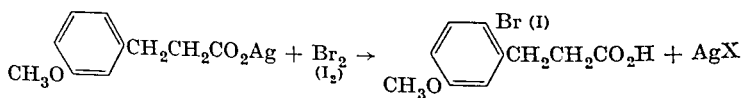
[59] Howton, Davis and Nevenzel, *J. Am. Chem. Soc.*, **74**, 1109 (1952).
[60] Allen and Wilson, *Org. Syntheses*, **26**, 52 (1946).
[61] Duschinsky and Rubin, *J. Am. Chem. Soc.*, **70**, 2546 (1948).
[62] Stoll and Rouvé, *Helv. Chim. Acta*, **34**, 98 (1951).
[63] Oldham, *J. Chem. Soc.*, **1950**, 100.

silver bromide, for 2-bromobicyclo[2.2.2]octane and silver bromide give the same product. By operating at $-10°$, it has been possible to isolate the expected bromide as well as the rearranged product.[69]
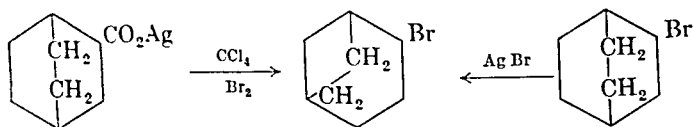
Silver salts of simple carboxylic acids having a tertiary α-carbon atom, such as silver trimethyl- and triphenyl-acetate, yield a variety of products when treated with bromine.[25] However, the silver salts of the complex alicyclic acids, adamantanedicarboxylic acid (IX)[70] and bicyclo[3.3.1]-nonan-9-one-1-carboxylic acid (X)[71] give the corresponding bromides in yields of 28 and 74%, respectively. These acids cannot be decarboxylated directly; the silver salt-halogen reaction, therefore, serves as an intermediate step in the preparation of the parent hydrocarbons.
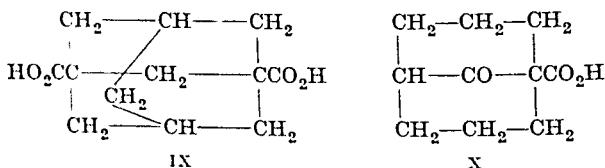
The reaction has been used successfully as a preliminary step in the synthesis of cantharadin from the silver salt (XI) of the 2,3-dimethyl ester of 2,3-dimethylcyclohexane-1,2,3,4-tetracarboxylic acid.[72] Treatment of this silver salt with bromine in carbon tetrachloride results in a lactone XII, formed by loss of methyl bromide from the primarily formed dibromide. Saponification and pyrolysis of the lactone gives a mixture of cantharic acid (XIII) and cantharadin (XIV). (Formulas on p. 345.)

When substituents other than alkyl or aryl are present in the α-position, the decarboxylation leads to a variety of products. The silver salts of α-halogen acids yield 1,1-dihalogenated hydrocarbons.[3,40] Many di-, tri-, and tetra-halogenated methanes, exemplified by such substances as

$$RCHXCO_2Ag + X'_2 \rightarrow RCHXX' + CO_2 + AgX'$$
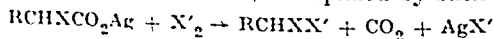
CH_2ClF, $CHBrClF$, CBr_2F_2 have been prepared by this reaction.[73] Any combination of hydrogen and halogen may be present in the silver salt,

$$RR'R''CCO_2Ag + X_2 \rightarrow RR'R''CX + CO_2 + AgX$$

XI → XII

1. Saponification
2. Pyrolysis

XIII   XIV

and X may be chlorine, bromine, or iodine. The yields vary widely (see Table V). Perfluoro acids give perfluoroalkyl halides.[73-80] A high

$$CF_3(CF_2)_nCO_2Ag + X_2 \rightarrow CF_3(CF_2)_nX + CO_2 + AgX$$

temperature is required because of the stability, mentioned earlier, of the trifluoroacetoxy radical toward decarboxylation. This is probably true to a smaller extent with the silver salts of various halogenated derivatives of acetic acid.

Other α-substituted acids that undergo the reaction include α-keto, α-hydroxy, and α-amino acids; α-keto acids give acyl halides whereas the hydroxy and amino acids lead to aldehydes. If the remaining hydrogen atom on the α-carbon atom of the hydroxy and amino acids is replaced by

$$RCOCO_2Ag + X_2 \rightarrow RCOX + CO_2 + AgX$$

$$RCHOHCO_2Ag + X_2 \rightarrow RCHO + CO_2 + AgX + HX$$

$$RCHNH_2CO_2Ag + X_2 \rightarrow RCHNH_2X + CO_2 + AgX$$
$$\xrightarrow{H_2O} RCHO + NH_4X$$

an alkyl group, ketones result. For the most part, these reactions are considered only in the original patent,[3] and little work has been done on their development. Heyns and Stange, however, have shown that the

[74] Hauptschein and Grosse, J. Am. Chem. Soc., 73, 2461 (1951).

[75] Hauptschein, Kinsman, and Grosse, J. Am. Chem. Soc., 74, 849 (1952).

[76] Brice and Simons, J. Am. Chem. Soc., 73, 4016 (1951).

[77] Henne and Finnegan, J. Am. Chem. Soc., 72, 3806 (1950).

[78] Haszeldine, J. Chem. Soc., 1951, 584.

[79] Hauptschein, Nodiff, and Grosse, J. Am. Chem. Soc., 74, 1347 (1952).

[80] Henne and Francis, J. Am. Chem. Soc., 75, 993 (1953).

silver salts of acylated α-amino acids give halogen derivatives that can be isolated.[81] On hydrolysis these products form the carbonyl derivative, amide, and hydrogen halide.

$$RCHNH(COR')CO_2Ag + X_2 \rightarrow RCHBr(NHCOR') + CO_2 + AgX$$

$$RCHBr(NHCOR') + H_2O \rightarrow RCHO + R'CONH_2 + HBr$$
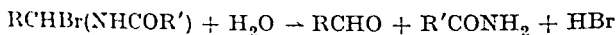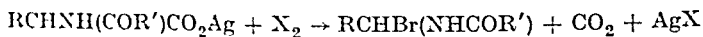
The silver salt of ethylmalonic acid, which may be considered an α-carboxy acid, gives a small yield of 1,1-dibromopropane together with some 1,1,1-tribromopropane; the tribromo derivative is presumably the result of some bromination before decarboxylation.[40] The potassium salts of the closely related alkyl α-carbethoxyacetic acids yield α-bromo[82] and α-chloro[53] fatty acid esters. Again there is some halogenation before

$$R'O_2CCHRCO_2K + X_2 \rightarrow R'O_2CHXR + CO_2 + KX$$
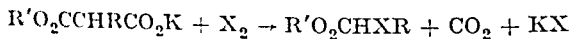
decarboxylation. The best yields result from compounds of intermediate chain length (6-8 carbon atoms).

The silver salts of unsaturated acids have not been useful in this reaction. Silver methacrylate added to bromine in carbon tetrachloride at 0° gives a polymeric product. Silver allylacetate yields a bromolactone.[40] Because of the ease with which acyl hypohalites add to the olefinic bond (see p. 350), a clear-cut reaction would not be expected. However, silver phenylpropiolate and iodine produce phenyliodoacetylene in excellent yield.[15]

Treatment of silver salts of α,ω-dicarboxylic acids with halogen leads to α,ω-dihalides.[3,20,40,51,63,84] Although this reaction is general, the yields of dihalide are poor with the lower members of the series. The formation of a bromo compound from silver succinate and bromine was observed by Bunge as early as 1870.[85] However, the yield is small even when the silver salt is added to a solution of bromine in carbon tetrachloride.[40] Silver glutarate and various alkyl-substituted derivatives give mainly γ-lactones though a small amount of dihalide is formed.[63]

$$AgO_2CCR_2CR_2CR_2CO_2Ag + X_2 \rightarrow \underline{CR_2CR_2CR_2CO_2} + CO_2 + 2AgX$$
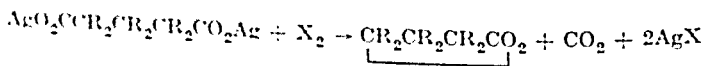
are obtained.[86]   With silver adipate there is some lactone formation, but a substantial yield of dibromide is obtained by the reverse addition procedure.[84]   The higher members of the series give moderately good yields of dihalides.   In the one instance in which a tricarboxy acid was used, the yield of trihalide was very small.[40]

Effect of the Halogen Employed. Bromine is most generally used in the Hunsdiecker reaction.   In the few instances in which chlorine has been employed the yields have been satisfactory.[3,52,73,75,83,87]   Iodine was normally used in a 1:2 molar ratio with the silver salts in the early work, and, consequently, the so-called Simonini ester was the main product. More recent work[87] has shown that an iodine-to-silver ratio of 1:1 affords substantial yields of the iodide, though some ester is produced.   In fact, the yield of iodide rises, and that of the ester falls as the ratio of iodine to silver is gradually increased from 1:2 to 1:1.   In the presence of excess iodine, the silver salts of the long-chain acids give good yields of the iodides.[8]   Excellent yields of iodides have also been obtained from the silver salts of fluoro and perfluoro acids,[73] but the use of iodine in the preparation of iodides by this reaction has not been investigated thoroughly. It may well serve as a method for producing alkyl iodides as well as bromides.

Effect of Temperature. The effect of temperature has not been studied systematically.   From available reports, it appears that the optimum temperature depends upon the silver salt used.   Bromobenzene, for example, is obtained in 80% yield when bromine is added to a sus-pension of silver benzoate in boiling carbon tetrachloride,[20] but the yield is insignificant when the reaction is carried out in the cold.[20,54]   Mehta and co-workers point out that carbon tetrachloride is a better solvent than chloroform for the reaction and indicate that its higher boiling point is responsible for the advantage.[87]   They show that better yields of long-chain alkyl halides are obtained in boiling than in cold carbon tetrachloride. On the other hand, cyclobutyl bromide is obtained only when the reaction is run in carbon tetrachloride below —20°.[35]   In some instances, operation at a low temperature is necessary because of the instability of the silver salts.   The silver salts of α-bromovaleric acid, β-bromopropionic acid, α-bromobutyric acid, and δ-bromovaleric acid, for example, are stable at 0° but not at room temperature.   Silver β-bromopropionate changes into β-propiolactone on drying in a desiccator at room temperature.[40] Nevertheless, these silver salts undergo the Hunsdiecker reaction at 0° to give fairly good yields of the corresponding bromides.

Effect of Solvent. Carbon tetrachloride is probably the best general

[86] Hauptschein, Stokes, and Grosso, *J. Am. Chem. Soc.*, **74**, 848 (1952).
[87] Mehta, Mehta, and Thosar, *J. Indian Chem. Soc., Ind. Ed.*, **3**, 166 (1940).

solvent for the reaction, although there are isolated instances in which other solvents produce better results. The production of n-propyl bromide from silver butyrate, for example, is carried out in nitrobenzene; if carbon tetrachloride is used, separation of the n-propyl bromide from the solvent is difficult because the two materials have approximately the same boiling point.[20]   Experiments carried out by Oldham and Ubbelohde have shown that good yields of undecyl iodide can be obtained in benzene (72–80%), carbon tetrachloride (70–78%), or petroleum ether (51–65%).[8] In the few instances recorded in which the silver salt was used in carbon disulfide, the yields were low.[25] Though Cason and Way prepared cyclobutyl bromide by operating in carbon tetrachloride at a low temperature,[35] the same halide has also been made by treatment of the mercuric salt of the acid with bromine in carbon disulfide.[5]   Dichlorodifluoromethane has been used successfully as a solvent in the preparation of cyclopropyl bromide[67] and ethyl 4-bromobicyclo[2.2.2]octane-1-carboxylate.[88] Tetrachloroethane was also used as a solvent in the former reaction, but the yield was poor.   Chloroform,[3,8] ether,[3,89] ethyl bromide,[65,65a] and trichloroethylene[62] have also been used. In trichloroethylene a surprisingly good yield of methyl ω-bromopentadecanoate was obtained from the requisite acid ester.   Treatment of the silver salts of perfluoro acids with halogens is usually carried out without a solvent,[52,73–75,77,78] but in one instance perfluorotributylamine has been used successfully.[76]

Salts of Other Metals.   Though silver salts have been generally used in this reaction, other salts have also been employed with varying success. Of these, the mercurous and mercuric salts have given the best results.[3–5] Thallium salts have also been satisfactory.[3]   With some substituted malonic acid half-esters, the potassium salts have been used with yields varying from 23 to 80%.[82,83]   The yields are highest when the substituent is n-butyl, n-hexyl, benzyl, or cyclohexyl and drop off rapidly when the number of carbons in the substituent is increased or decreased.   Trifluoroacetic acid gives poorer yields of trifluoromethyl iodide when the sodium, potassium, barium, mercury, or lead salt is employed in place of the silver salt.   The reaction is carried out in a steel autoclave at a high temperature.[74]

Since esters are usually secured more easily by other procedures, the reaction has little value as a synthetic method. It has been of primary interest in connection with the mechanism of formation and decomposition of the complex, and because of a useful synthesis in which the complex is used, viz., the Prévost reaction (see p. 350).

Those silver salts that undergo the Hunsdiecker reaction readily also, in general, undergo the Simonini reaction. Only in the case of silver salts of saturated monocarboxylic acids is any difference discernible. The difference appears to be due to an ability of the primarily formed hypoiodites to give complexes or coordination compounds with the silver salt, an ability that apparently is not shared to any great degree by the acyl

$$RCO_2Ag + RCO_2I \rightarrow RCO_2Ag \cdot RCO_2I$$
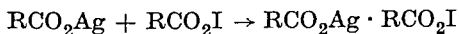
hypobromites though a small quantity of ester is formed occasionally. Acyl hypoiodites also form stable coordination complexes with tertiary bases such as pyridine and α-picoline.[90]

In the dibasic acid series, the products obtained by the Simonini procedure are comparable to those obtained with bromine. Silver oxalate yields only carbon dioxide and silver halide.[43,49] Silver malonate produces carbon dioxide, but no other product has been identified.[49] Silver succinate regenerates succinic acid and forms a little maleic anhydride, while silver glutarate and various substituted derivatives give γ-lactones in fair yields (40%). The method has been suggested as a preparative procedure for γ-lactones.[91-93] Similar products are obtained with bromine.[63] Silver adipate yields a small amount of polymerized δ-valerolactone.[49] The reaction with homologs higher than adipic acid has not been investigated.

Unsaturated acids do not give clear-cut results. Although the intermediate complex is formed in many cases and carbon dioxide is lost in the decomposition, the only other products identified are the unchanged acid or its anhydride.[43,49] Hydroxy acids yield aldehydes or ketones. This reaction, first reported by Herzog and Leiser,[89] proceeds as well with bromine as with iodine.[3] Thus, formaldehyde is formed from glycolic acid, while mandelic acid yields benzaldehyde.

In the aromatic series, the reaction has no value. Silver benzoate gives a variety of products including ester, halide, and halogenated benzoic acid.[49] Silver phthalate leads to phthalic anhydride, whereas silver hexahydrophthalate gives no identifiable products.[49]

[90] Zingaro, Goodrich, Kleinberg, and VanderWerf, *J. Am. Chem. Soc.*, **71**, 575 (1949).
[91] Windaus and Klänhardt, *Ber.*, **54**, 581 (1921).
[92] Windaus, Klänhardt, and Reverey, *Ber.*, **55**, 3981 (1922).
[93] Goldschmidt and Gräfinger, *Ber.*, **68**, 279 (1935).

Thermal Cleavage of Iodine Triacyls

A reaction somewhat similar to the Simonini reaction takes place when a silver salt and iodine react in a 3 : 2 molar ratio.[8] The product contains positive, trivalent iodine but no silver. It is presumably an iodine triacyl, which decomposes thermally to produce both ester and alkyl

$$I(OCOR)_3 \xrightarrow{\text{Heat}} RCO_2R + RI + 2CO_2$$
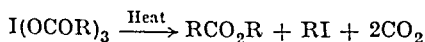
halide. Heating in the presence of excess iodine gives the alkyl iodide only.

$$I(OCOR)_3 + I_2 \rightarrow 3RI + 3CO_2$$
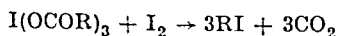
Addition Reactions of Acyl Hypohalites
(Prévost Reaction)

The intermediates formed in the Simonini and Hunsdiecker reactions, $RCO_2Ag \cdot RCO_2I$ and RCO_2X, respectively, will react with olefins, acetylenes, and sufficiently reactive phenyl groups. The addition to olefins was first reported by Birckenbach, Goubeau, and Berninger,[21] who treated silver acetate with iodine in ether solution, removed the silver iodide formed, and treated the filtrate with cyclohexene. The acetate of 2-iodocyclohexanol resulted. The same substance had been obtained by Brunel some years earlier in a similar reaction with mercuric acetate,

$$CH_3CO_2Ag + I_2 + \underset{}{\bigcirc} \xrightarrow[-80°]{(C_2H_5)_2O} \underset{OCOCH_3}{\bigcirc}{}^{I} + AgI$$
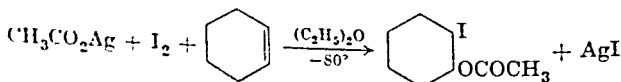
iodine and cyclohexene.[91] However, the method has been developed mainly by Prévost,[9-11,13,14] and the reaction is generally known by his name. Its chief use lies in the preparation of 1,2-glycols.

When the Simonini complex obtained from silver benzoate and iodine is treated in benzene solution with an olefin, silver iodide precipitates and the dibenzoate of a 1,2-glycol is formed. Although the complex from

$$C_6H_5CO_2Ag \cdot C_6H_5CO_2I + RCH{=}CH_2 \rightarrow RCH(OCOC_6H_5)CH_2OCOC_6H_5$$
$$+ AgI$$

Although benzoates are recommended, silver salts of acetic,[10,22] propionic,[22] and butyric acids[20,22] have also been used, especially in the preparation of the halo esters. Indeed, the second phase of the reaction of an olefin with silver acetate and an equimolar amount of iodine in benzene solution is slow, and the diester is accompanied by iodo acetates which are difficult to remove.[10]

The reaction also proceeds with silver salts of dicarboxylic acids. Thus, silver succinate, iodine, and cyclohexene in ether solution give di-2-iodocyclohexyl succinate. A small quantity of polymeric diester

$$
\begin{array}{c} CH_2CO_2Ag \\ | \\ CH_2CO_2Ag \end{array} + I_2 + 2 \;\bigcirc\; \rightarrow \begin{array}{c} CH_2CO_2C_6H_{10}I\text{-}o \\ | \\ CH_2CO_2C_6H_{10}I\text{-}o \end{array} + 2AgI
$$
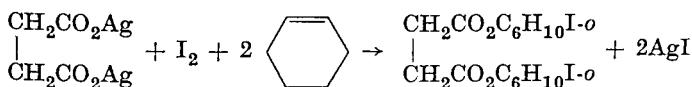
$(C_{10}H_{14}O_4)_n$ is formed simultaneously. Silver salts of oxalic and phthalic acids and even silver carbonate undergo similar reactions.[95]

Silver 3,5-dinitrobenzoate has been suggested as a reagent for identification of olefins. Simple olefins like ethylene and propylene give the 3,5-dinitrobenzoate of the iodohydrin when treated with equimolar amounts of iodine and silver 3,5-dinitrobenzoate.[96] When unsymmetrical

$$3,5\text{-}(NO_2)_2C_6H_3CO_2Ag + I_2 + RCH\!\!=\!\!CHR' \rightarrow$$
$$RCHICH[OCOC_6H_3(NO_2)_2]R' + AgI$$
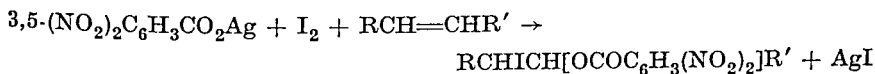
olefins are used, the halogen appears exclusively on the less highly substituted carbon atom. This mode of addition, however, is not general, for preformed hypohalites from acetic, butyric, and benzoic acids add to allyl halides to give good yields of 2,3-dihalogenated propyl esters.[20,97]

Bromine or chlorine can be used in place of iodine.[14,22,51] With these halogens, however, it is advantageous to carry out the reaction in carbon tetrachloride rather than benzene, to avoid the undesirable side reaction with the latter solvent which leads to the formation of phenyl benzoate.[14] In the absence of detail in Prévost's papers, one is inclined to favor carbon tetrachloride as a solvent for all of the halogens. However, benzene has been used successfully by other experimenters.[98,99]

Studies on the addition of the complex from silver benzoate and iodine to butadiene have shown that the primary addition is mainly 1:2. Fractionation of the glycols obtained from the action of a limited quantity of the complex with butadiene gave 80% 1,2-glycol and 4% 1,4-glycol.[11]

The reaction has been applied to the mixture of monohydric phenols

[95] Birckenbach, Goubeau, and Kolb, *Ber.*, 67, 1729 (1934).
[96] Halperin, Donahoe, Kleinberg, and VanderWerf, *J. Org. Chem.*, 17, 623 (1952).
[97] Edwards and Hodges, *J. Chem. Soc.*, 1954, 761.
[98] Hershberg, *Helv. Chim. Acta.*, 17, 351 (1934).
[99] Niemann and Wagner, *J. Org. Chem.*, 7, 227 (1942).

on the silver salts of the unhalogenated acids.[15] Silver β-(p-nitrophenyl)-propionate, however, gives p-nitrophenethyl bromide in excellent yield.[16]

$$O_2N\langle\ \rangle CH_2CH_2CO_2Ag + Br_2 \rightarrow O_2N\langle\ \rangle CH_2CH_2Br + CO_2 + AgBr$$
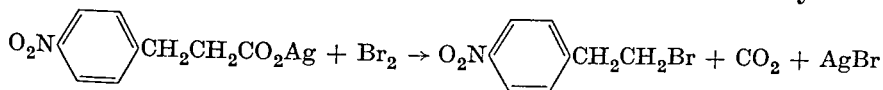
Although the method has little practical value for reasons that will appear below, it has been used to prepare a series of halogenated alkoxyphenyl fatty acids of the general formula.[18]

$$RO\langle\ \rangle(CH_2)_nCO_2H$$
$$X$$
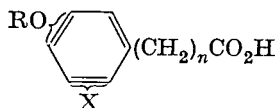
The preparation of the silver salt of the acid to be halogenated is unnecessary. It is sufficient to use dry silver acetate in combination with the halogen; the acyl hypohalite first formed is the active halogenating agent.[17,18] The reaction is carried out in acetic acid or carbon tetrachloride. It proceeds as indicated only when a phenyl group active

$$RO\langle\ \rangle(CH_2)_nCO_2H + CH_3CO_2Ag + X_2 \rightarrow$$

$$RO\langle\ \rangle^X(CH_2)_nCO_2H + AgX + CH_3CO_2H$$
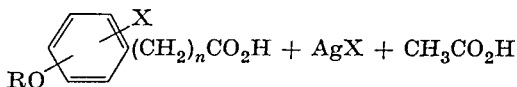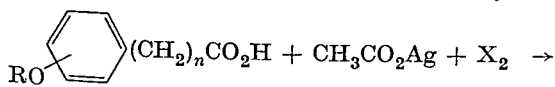
toward electrophilic substitution is present. It is, therefore, quite limited in application. The method is preferred to the mercuric acetate-iodine procedure because of the difficulty of removing mercuric iodide from organic solvents in which it is soluble; silver iodide can be removed quantitatively by filtration.

The silver salts of a variety of carboxylic acids react with iodine in the presence of benzene to yield, among other products, iodobenzene and/or the phenyl ester of the carboxylic acid.[103] The yield of iodobenzene is highest from silver o-nitrobenzoate. In the absence of benzene, however, this silver salt on treatment with bromine gives a 95% yield of o-nitrobromobenzene—the Hunsdiecker product. Benzene, therefore, is not a good solvent for reactions involving acyl hypohalites because it enters into competition for the halogen. When the acyl hypohalite undergoes the Hunsdiecker reaction sufficiently rapidly, benzene can be used as a solvent. This is the case when R is a long chain such as n-$C_{11}H_{23}$ or n-$C_{17}H_{35}$.

The reaction between silver trifluoroacetate and iodine to yield carbon dioxide, silver iodide, and trifluoromethyl iodide does not occur appreciably

[103] Birckenbach and Meisenheimer, *Ber.*, 69, 723 (1936).

below 100°,[77] and silver trifluoroacetate-halogen is, therefore, a useful halogenating agent. Excellent yields of bromo- and iodo-benzenes containing methyl, halogen, methoxyl, amino, dimethylamino, and carboxyl groups as substituents are obtained by this procedure.[19,52] Benzene is so deactivated, however, by the introduction of a nitro group that the normal Hunsdiecker product, CF_3I, is produced in 75% yield when nitrobenzene is treated with silver trifluoroacetate and iodine.

Normally no solvent is used in these reactions though carbon tetrachloride has been used successfully.[52] Nitrobenzene is often a suitable solvent.

The halogen enters in the *para* position to the group already present in the benzene derivative if the latter normally directs to that position. Infrared analyses indicate that a small amount of the *ortho* isomer is usually present. Benzoic acid is halogenated in the *meta* position, and there is no indication of *ortho* or *para* halogenation.

Although silver trifluoroacetate-halogen is not so powerful a halogenating agent as silver perchlorate-halogen, it possesses certain specific advantages.[19] Trifluoroacetic acid, formed in the reaction, is volatile and is easily removed by distillation. The danger attending the use of silver perchlorate is avoided. Silver trifluoroacetate is more soluble in organic solvents than silver trichloroacetate, acetate, perchlorate, or sulfate.[19]

It has been demonstrated that the Simonini complex from silver benzoate reacts with acetylenes to give excellent yields of iodoacetylenes. With phenylacetylene, the formation of phenyliodoacetylene is quantitative and benzoic acid and silver benzoate have been isolated in quantities corresponding to the following equation.[12] Acetylene itself reacts with

$$C_6H_5CO_2Ag \cdot C_6H_5CO_2I + C_6H_5C \equiv CH \rightarrow C_6H_5C \equiv CI + C_6H_5CO_2H + C_6H_5CO_2Ag$$
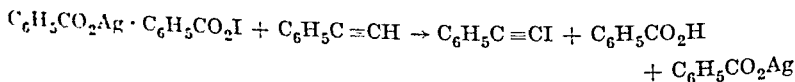
either one or two molecules of the complex to give iodo- and diiodoacetylene, respectively.[12]

It is not necessary to isolate the complex; addition of the acetylene derivative to the complex formed in benzene is satisfactory. However, the use of benzene as a diluent is not practical with chlorine or bromine because it takes part in the reaction. Carbon tetrachloride is satisfactory. Thus, the treatment of silver benzoate in carbon tetrachloride with bromine, chlorine, or iodine followed by addition of 1-heptyne gives good yields of the respective haloacetylenes.[14]

Prévost assumes that the Simonini complex is formed with chlorine and bromine in the same manner as with iodine.[14] Such a complex has not been isolated with these halogens, nor is it necessary to assume that it

forms. The reaction could proceed equally well with the intermediate acyl hypohalite.

$$RCO_2X + R'C \equiv CH \rightarrow R'C \equiv CX + RCO_2H$$
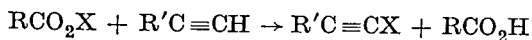
EXPERIMENTAL PROCEDURES
Preparation of Silver Salts

Two general methods are available for preparing the silver salts. The simplest and most direct method is the reaction between the potassium or sodium salt of the acid and silver nitrate. For acids of low molecular weight and for most dibasic acids, this is the most satisfactory method. For the higher acids (above C_8) especially when fairly large quantities are employed, it has been suggested that freshly prepared silver oxide be used.[4] Reaction of the potassium or sodium salts of the higher acids with silver nitrate leads to voluminous precipitates which are difficult to filter. For acids that are sparingly soluble in water the use of ethanol-water mixtures is recommended. For perfluoro acids unstable in water (undecafluorocyclohexanecarboxylic acid, for example), the use of silver oxide is a necessity. With these acids the reaction is run in perfluorobutyl ether as a solvent. A representative preparation by each of these methods follows. It is essential to the success of the subsequent reactions with the halogens to have the silver salts perfectly dry.

Silver Laurate.[54] Hot solutions of 50 g. of silver nitrate in 100 ml. of water and 59 g. of lauric acid in 200 ml. of 1.45 N potassium hydroxide are added simultaneously to 100 ml. of hot water with stirring. The addition is controlled so that approximately equivalent quantities of the reactants are present at all times. The precipitated silver salt is collected on a filter, washed with water and acetone, and air-dried. This material is powdered and then dried in a vacuum at 60° over phosphorus pentoxide. The yield is 85 g. (94%).

Silver Methyl Octadecanedioate.[4] The silver oxide precipitated by the admixture of water solutions of 270 g. of silver nitrate and 150 g. of potassium hydroxide is washed free from alkali. The moist oxide is added to 520 g. of molten methyl hydrogen octadecanedioate and stirred vigorously while boiling water is added. The silver salt formed is collected on a filter, washed with hot ethanol, dried, finely powdered, and redried. The yield is 637 g. (99%).

Substituted Silver Benzoates.[17,90] The organic acid is dissolved in hot ethanol, and a hot aqueous solution of sodium carbonate is added until the solution is basic to litmus. Nitric acid is then added dropwise until the solution is just acid to litmus. Any solid present is filtered, and a hot aqueous solution of an equivalent amount of silver nitrate is added

to the filtrate. The silver salt is removed by filtration, washed with distilled water and ethanol, and dried at 70°.

Silver Bicyclo[3.3.1]nonan-9-one-1-carboxylate.[71] A solution of 20 g. of bicyclo[3.3.1]nonan-9-one-1-carboxylic acid in 50 ml. of methyl alcohol is titrated to the end point of phenolphthalein with a solution of potassium hydroxide in methyl alcohol. A solution of 18.6 g. of silver nitrate in 20 ml. of water and 50 ml. of methyl alchol is added dropwise with stirring; the silver salt is collected on a filter, washed with methyl alcohol, and dried at 70° under vacuum for eighteen hours. The product contains potassium nitrate but gives results in subsequent reaction that are as satisfactory as those obtained with the silver salt prepared in aqueous solution.

Silver Undecafluorocyclohexanecarboxylate.[76] To a solution of 9.05 g. of undecafluorocyclohexanecarboxylic acid in 66 ml. of perfluorobutyl ether is added 3.22 g. of alkali-free silver oxide. The mixture is shaken intermittently in the dark over a three-day period. Only a trace of unreacted silver oxide remains. The silver salt, 11.35 g. (94.3%), is collected on a Pyrex filter cone, washed with perfluorobutyl ether, and dried at 50° for ten hours. The salt is a white, light-sensitive, crystalline, non-hygroscopic material, soluble in water. All operations in its preparation are carried out in the dark.

Products Formed by the Hunsdiecker Reaction

Methyl 5-Bromovalerate. The preparation of this material in 52–54% yield from methyl hydrogen adipate is described in *Organic Syntheses*.[60]

n-Propyl Bromide.[20] A solution of 40 g. of bromine in 250 ml. of freshly distilled nitrobenzene is added with vigorous shaking and cooling to 53.5 g. of silver butyrate. In about one minute, the bromine has reacted and the solution is yellow in color. This is followed by sudden, turbulent evolution of carbon dioxide, and the solution becomes quite warm. When gas evolution ceases, the silver bromide is removed by filtration and the filtrate is distilled through a Widmer column. There is obtained 17.2 g. (61%) of n-propyl bromide, 2.7 g. of butyric acid, and a trace (0.5 g.) of n-propyl butyrate.

n-Heptyl Bromide.[4] To a suspension of 102.5 g. of mercuric octanoate in 100 ml. of carbon disulfide (dried over phosphorus pentoxide) is added dropwise 22 ml. of dry bromine. There is a smooth evolution of carbon dioxide. When the initial reaction has subsided, the mixture is warmed for a short time on the steam bath. The mercuric bromide is removed by filtration and washed well with carbon disulfide. The solvent is removed from the filtrate and washings, and the residue is fractionated

under reduced pressure to yield 55.7 g. (75%) of *n*-heptyl bromide, b.p. 74°/18 mm. A higher boiling fraction (133-137°/18 mm.) is octanoic acid (6.1 g., 10%).

_n_-Undecyl Bromide.[54] To a suspension of 46 g. of silver laurate in 200 ml. of carbon tetrachloride (dried over phosphorus pentoxide) is added slowly, with stirring and cooling, 7.5 g. of dry bromine in 20 ml. of dry carbon tetrachloride. The mixture is heated gradually until the evolution of carbon dioxide ceases and is then held for a short time at its boiling point. The silver bromide is removed by filtration, placed in an extraction thimble, and extracted for one to two hours, the filtrate being used as an extracting solvent. After the carbon tetrachloride solution is washed with dilute aqueous sodium hydroxide and water, the solvent is removed and the residue distilled to give 24 g. (67%) of undecyl bromide, b.p. 131–134°/15 mm.; 5.5 g. (18%) of lauric acid can be recovered from the alkaline wash liquid.

1,4-Dibromobutane.[84] To a well-stirred solution of 48 ml. of dry bromine in 250 ml. of dry carbon tetrachloride is added (with the exclusion of water) 163 g. of silver adipate. The addition is made in small portions over a seven-hour period. After the addition of each portion of silver salt, the reaction is started by warming to 50° and is allowed to continue until the evolution of carbon dioxide ceases. Heating is continued for one-half hour to complete the reaction. The silver bromide is removed by filtration and washed thoroughly with ether. The carbon tetrachloride and ether solutions are combined and decolorized by shaking with a saturated solution of sodium bisulfite; the decolorized solution is shaken with 10% aqueous potassium hydroxide solution, any emulsion that forms being broken with sodium chloride. The solution is finally washed with sodium chloride solution and dried. The solvents are removed through a fractionating column at ordinary pressure, and the residue is distilled. The 1,4-dibromobutane distils at 78-81°/11 mm.; the yield is 58 g. (58%).

1,10-Dibromodecane.[3] A mixture of 40 g. of the silver salt of dodecanedicarboxylic acid and 100 ml. of carbon tetrachloride is treated gradually with 9 ml. of bromine. The silver bromide that separates during the reaction is removed by filtration and washed with hot carbon tetrachloride. The filtrate and washings are combined and shaken with sodium bicarbonate solution to remove any free acid. The solvent is removed and the residue distilled to give 16.8 g. (about 60%) of 1,10-dibromodecane, b.p. 190–195°, m.p. 35–36°.

Methyl 17-Bromoheptadecanoate.[4] To a suspension of 673 g. of the silver salt of methyl 17-carboxyheptadecanoate in 750 ml. of carbon tetrachloride is added, with cooling and stirring, 81 ml. of bromine.

The mixture is finally warmed on a water bath for a short time, and the silver bromide formed is removed by filtration. When the filtrate is cooled to 0°, 58 g. of the monoester acid separates. The remainder can be removed by shaking the solution with dry potassium carbonate; aqueous alkalies form emulsions that are difficult to deal with. Removal of solvent and distillation gives 432 g. (75%) of methyl 17-bromo-heptadecanoate, b.p. 212–214°/2.5 mm.

Trifluoromethyl Iodide.[77] A mixture of 66 g. (0.3 mole) of finely ground silver trifluoroacetate and 81 g. (0.32 mole) of powdered iodine was placed in a horizontally held tube, 25 mm. in diameter and 25 cm. long; this tube was sealed at one end while the other end was connected to a wide trap cooled in ice water and backed by two traps cooled in solid carbon dioxide (Dry Ice) and a small water bubbler which served to show the rate of evolution of the carbon dioxide. The ice trap collected a fine sublimate of iodine and prevented clogging of the solid carbon dioxide (Dry Ice) traps, the first of which collected practically all of the trifluoro-methyl iodide.

The mixture of silver salt and iodine was heated cautiously with a gas burner, starting at the closed end. The decomposition is smooth at about 100°, but tends to propagate spontaneously and escape control when the heating is not done patiently. The bubbling of carbon dioxide is used as an indicator for the speed at which the burner can be moved along the tube. With the small equipment used, it took ninety minutes to complete the reaction. The crude trifluoromethyl iodide amounted to 47 g. (85%). A series of larger runs gave an average yield of 87%. Fractional distillation gave a product boiling at 21.8°.

Trifluoromethyl iodide is conveniently stored in glass ampules. Exposed to light, it slowly becomes pink, then purple.

A comparable procedure is described by Haszeldine.[78]

Cyclobutyl Bromide.[35] To a flask equipped with a mercury-seal stirrer is added 560 ml. of carbon tetrachloride (dried over phosphorus pentoxide), and 50 ml. of carbon tetrachloride is distilled in order to dry the flask thoroughly. The system is protected with a drying tube and, after addition of 85.2 g. (0.534 mole) of bromine (dried over phosphorus pentoxide), the mixture is cooled to −25° with stirring. To this is added 111 g. (0.534 mole) of the silver salt of cyclobutanecarboxylic acid. The salt is added over a period of about fifty minutes through a wide rubber connection from the flask in which it had been dried. After an induction period of five to twenty minutes, a vigorous evolution of carbon dioxide sets in and continues as the remainder of the silver salt is added. Evolution of carbon dioxide is accompanied by the evolution of heat, but the temperature is easily maintained at −25 to −20° with a solid carbon

dioxide-acetone bath. After addition is complete, the mixture is stirred briefly until gas evolution becomes slow and then is allowed to warm to room temperature with stirring. When gas evolution has ceased, the silver bromide is removed and washed with carbon tetrachloride. The filtrate is washed with 2 N sodium hydroxide and water and then dried over calcium chloride. The combined alkaline extracts from a total of 2.6 moles of silver salt yield only 2.2 g. of acidic material.

The carbon tetrachloride solution is flash-distilled through a 1-meter column packed with glass helices and equipped with heated jacket and partial reflux head. During flash distillation, the volume of solution in the distilling flask is kept sufficiently large so that the mole fraction of cyclobutyl bromide is kept below 0.2. This avoids loss of bromide, and the carbon tetrachloride is collected at 76.9°. After all the carbon tetrachloride solution has been added, removal of solvent is continued and an intermediate fraction (7.9 g.), b.p. 76.9–108.2°, is collected. Cyclobutyl bromide (36 g., 50%) is collected at 108.2–108.3°; n_D^{20} 1.4801, d^{20} 1.434, MR_D 26.75 (calculated 26.72). There is 15 g. of distillation residue. By redistilling the intermediate fractions from several runs and stripping the residues in a vacuum, the total yield is raised to 53%. The same yield is obtained in larger (1.9 mole) runs.

p-Nitrobromobenzene.[16] To a suspension of 34 g. of silver p-nitrobenzoate in 500 ml. of carbon tetrachloride 20 g. of bromine is added dropwise at room temperature. The deep-red solution obtained at the end of the addition is heated slowly to boiling; there is no evolution of carbon dioxide below the reflux temperature. The solution is boiled for three hours, during which time the color gradually fades. The hot solution is filtered, and the filtrate is washed with sodium bisulfite and sodium bicarbonate solutions. Acidification of the sodium bicarbonate extract produces 2 g. (10%) of p-nitrobenzoic acid. Evaporation of the carbon tetrachloride leaves 20 g. (74%) of crystalline p-nitrobromobenzene, m.p. 126–127°.

Ethyl α-Bromo-β-phenylpropionate.[82] To a solution of 37.5 g. (0.15 mole) of diethyl benzylmalonate in 100 ml. of absolute ethanol is added, with stirring, a solution of 8.7 g. (0.15 mole) of potassium hydroxide in 100 ml. of absolute ethanol. The solution is allowed to stand at room temperature for four to twelve hours; the pH of the final mixture has a value between 7 and 8. Any solids that have formed (assumed to be the dipotassium salt) are removed by filtration. The ethanol is distilled until a thick syrup remains. The last traces of ethanol are removed in vacuum, and the resulting crystals of the potassium salt of the half ester of benzylmalonic acid are placed in a vacuum desiccator for twelve hours.

The dried, finely powdered potassium salt is mixed with 100 ml. of

carbon tetrachloride. The ice-cold mixture is stirred vigorously while a solution of 25 g. (0.15 mole) of bromine in 50 ml. of carbon tetrachloride is added dropwise over a period of two to four hours. The bromine is decolorized rapidly at the start of the reaction, but persists after all of the bromine solution has been added. The mixture is filtered, and the solvent is removed in a current of air. The residue is distilled under reduced pressure to give colorless, strongly lachrymatory ethyl α-bromo-β-phenyl-propionate 38 g. (80%), b.p. 155–159°/15 mm.

Products Formed by the Simonini Reaction

Because the esters produced by the Simonini reaction are usually procured more easily by other procedures, the reaction has not been developed as a synthetic method. Consequently, no detailed procedure is available. The following example is typical of the experimental work on this reaction.

Benzyl Phenylacetate.[49] When 24.3 g. of silver phenylacetate and 12.7 g. of iodine are mixed in ether, an exothermic reaction sets in and the ether boils. The solvent is removed by distillation and the residue heated for one hour at 80°. The residue is extracted with ether from which 1.35 g. (10%) of phenylacetic acid and 9.35 g. (68%) of benzyl phenyl-acetate are obtained.

Products Formed by the Prévost Reaction

2-Iodocyclohexyl Acetate.[21] To 8.2 g. (0.1 mole) of cyclohexene in ether is added 25.4 g. (0.1 mole) of iodine and 16.6 g. (0.1 mole) of silver acetate. An exothermic reaction ensues, and the ether begins to boil. The silver iodide formed in the reaction is removed by filtration, the solvent removed, and the residue fractionated. The product, 2-iodocyclohexyl acetate, obtained in 80% yield, boils at 120°/12 mm.

3-Phenyl-1,2-propyleneglycol Dibenzoate.[98] To 11.8 g. of allylbenzene in 300 ml. of dry benzene is added 45.8 g. of silver benzoate and 25.4 g. of iodine (or the corresponding amount of the silver benzoate-iodine complex). This mixture is heated under reflux for fifteen hours with the careful exclusion of moisture. The reaction mixture is cooled, the precipitated silver iodide removed by filtration, and the filtrate washed several times with aqueous sodium bicarbonate solution and finally with water. The solution is dried, the benzene removed, and the reddish-brown residue crystallized in an ice-salt bath. Trituration with petroleum ether is necessary to induce crystallization. The product is collected on a filter, washed with petroleum ether, and dried. The yield of crude product melting at 70–71° is 28.5 g. (85%). The pure product

melts at 74–75°. Hydrolysis to the glycol in a yield of about 85 effected with sodium hydroxide.

1,2-Hexadecanediol.[99] Iodine (10.6 g.) in 100 ml. of dry ben is added, with shaking, to a suspension of 26.5 g. of silver benzoat 150 ml. of benzene. To this solution is added, slowly and with shak 10.5 g. of 1-hexadecene in 50 ml. of benzene. The mixture is he under reflux for one hour, cooled, and filtered, and the filtrate free solvent. The residual glycol dibenzoate is saponified by heating u reflux for three hours with 12 g. of potassium hydroxide in 75 ml ethanol and 25 ml. of water. The glycol is recovered by pouring hydrolysate into 500 ml. of hot water. After cooling, the crude glyc collected, recrystallized twice from methanol, then from ligroin (l 60–70°), and finally from methanol to give 4 g. (33%) of 1,2-hexadecaned m.p. 73–73.6°.

By a similar procedure, 288 g. of 1-octadecene, 620 g. of silver benzo and 290 g. of iodine give 239 g. (73%) of 1,2-octadecanediol, m 79–79.5°.

2-Bromocyclohexyl Benzoate.[22] To a suspension of 11 g. of sil benzoate in 75 ml. of carbon tetrachloride cooled to −10° is added one-h of a solution of 7.3 g. of bromine in 18 ml. of carbon tetrachloride a one-half of a solution of 3.8. g of cyclohexene in 15 ml. of the same solve After ten or fifteen minutes, the remainder of the bromine and cyclohexe solutions is added. The precipitate is removed by filtration and wash with carbon tetrachloride. The combined filtrates are washed first wi dilute aqueous sodium hydroxide to remove any benzoic acid and the with water. The solution is dried over calcium chloride, the solvent removed, and the residue is recrystallized from petroleum ether. Th product (42%) melts at 64–64.5°.

Products Formed by Substitution Reactions of Acyl Hypohalites

β-(2-Iodo-5-methoxyphenyl)propionic Acid. *Method* 1.[18] To stirred solution of 0.1 mole of β-(3-methoxyphenyl)propionic acid in 10 ml. of acetic acid there is added alternately, in small portions, 25.4 g (0.1 mole) of powdered iodine and 16.6 g. (0.1 mole) of silver acetate Iodination proceeds rapidly at room temperature. The iodinated mixture is stirred for one hour at room temperature after the addition is complete filtered, and the filtrate is diluted with water. The oily product that separates is extracted with ether, the ether extracts are washed free of acetic acid, and the iodinated acid is purified by recrystallization from a mixture of chloroform and petroleum ether. The product obtained in 30% yield melts at 109–110°.

Method II.[18]   To a suspension of 14.3 g. (0.05 mole) of silver β-(3-methoxyphenyl)propionate in 100 ml. of anhydrous carbon tetrachloride in a 500-ml. three-necked flask equipped with an efficient stirrer, there is added dropwise at room temperature 25.4 g. (0.1 mole) of iodine dissolved in carbon tetrachloride.   The iodine reacts immediately and silver iodide precipitates.   After the addition is complete, the mixture is stirred for one hour, the silver iodide is separated, and the solvent is removed under reduced pressure.   The iodinated acid is purified by crystallization from chloroform-petroleum ether.   The yield is 90%, m.p. 109–110°.

p-Diiodobenzene.[19]   A mixture of 12 ml. (0.11 mole) of iodobenzene and 4.4 g. (0.02 mole) of silver trifluoroacetate is heated to 100° in a small flask fitted with a condenser which is connected by rubber tubing to liquid air traps.   The mixture is cooled to room temperature and 5.1 g. (0.02 mole) of powdered iodine is added.   There is an immediate precipitation of silver iodide.   The mixture is heated rapidly to 160°, cooled to room temperature, and filtered.   The liquid air traps contain only a small amount of trifluoroacetic acid.   Distillation of the solution gives 1.85 g. (80%) of trifluoroacetic acid, b.p. 71–72°, iodobenzene, b.p. 80°/12 mm., and 5.1 g. (77%) of *p*-diiodobenzene, which may be crystallized from ethanol as plates, m.p. 128°.

4-Iodoveratrole.[53a]   A mixture of 110 g. (0.5 mole) of silver trifluoroacetate and 69 g. (0.5 mole) of dry veratrole was placed in a dry, 1-l. flask equipped with stirrer and dropping funnel.   A chloroform solution of iodine was prepared from 127 g. (0.5 mole) of iodine and about 750 ml. of chloroform.   The chloroform solution was added during one-half hour, after which any undissolved iodine was added as the solid. (Alternatively, sufficient chloroform to dissolve the iodine, about 15 : 1, may be used.)   After stirring for two hours, the mixture was filtered and the precipitate washed with 100 ml. of chloroform.   The solvent was removed and the residue distilled.   The yield of product boiling at 152–155°/15 mm. was 112 g. (85%).   Redistillation gave a pale-yellow product, n_D^{25} 1.6117, which after crystallization from ethanol melted at 34–35°.

TABULAR SURVEY OF SILVER SALT-HALOGEN REACTIONS

In Tables I–XVII are listed all the examples of silver salt-halogen reactions that have been noted in a survey of the literature through 1954.* In general, the substances are arranged in increasing order of molecular weight.   Most of the tables provide the following information: silver salt employed, solvent, main product of the reaction, yield, and reference. A separate column for the halogen used is not included since the formula of the product will make this clear.

* The bibliography in reference 2a covers the literature through June 1955.

TABLE I

FORMATION OF ALKYL HALIDES FROM ALIPHATIC MONOCARBOXYLIC ACIDS

Acid	Solvent	Main Product	Yield, %	Reference
CH_3CO_2H	None	CH_3Br	—	56
	None	CH_3Br	80	3
	CCl_4	CH_3Br	69	20
$n\text{-}C_3H_7CO_2H$	$C_6H_5NO_2$	$n\text{-}C_3H_7Br$	61	20
$n\text{-}C_4H_9CO_2H$	CS_2	$n\text{-}C_4H_9Br$	31	25
$C_2H_5CH(CH_3)CO_2H$*	$C_6H_5NO_2$	$C_2H_5CHClCH_3$	74 crude	25
	CS_2	$C_2H_5CHBrCH_3$	14	25
$(CH_3)_3CCO_2H$	CS_2	No definite products		25
$(CH_3)_2CHCH_2CO_2H$	CS_2	$(CH_3)_2CHCH_2Br$	15	25
$n\text{-}C_5H_{11}CO_2H$	CCl_4	$n\text{-}C_5H_{11}Br$	92†	63
$n\text{-}C_3H_7CH(CH_3)CO_2H$	CCl_4	$n\text{-}C_3H_7CHBrCH_3$	55–65	66
$(C_2H_5)_2CHCO_2H$	CCl_4	$(C_2H_5)_2CHBr$	76	66
$(CH_3)_2CHCH_2CH_2CO_2H$	CS_2	$(CH_3)_2CHCH_2CH_2Br$	42	25
$(CH_3)_3CCH_2CO_2H$	$C_6H_5NO_2$	$(CH_3)_3CCH_2Br$	62	33
	CCl_4	$(CH_3)_3CCH_2Br$	83†	63
$n\text{-}C_7H_{15}CO_2H$	CCl_4	$n\text{-}C_7H_{15}Br$	79	30
$n\text{-}C_4H_9CH(C_2H_5)CO_2H$‡	CCl_4	$n\text{-}C_4H_9CHBrC_2H_5$§	30–50	24, 26, 28

* The (+) acid gives an optically inactive chloride.
† The yield is not based on pure isolated material, but on a quantitative determination of bromine present in the neutral fraction of the reaction product.
‡ The silver salt was added to bromine in carbon tetrachloride, the reverse of the normal addition.
§ Both optically active forms of the silver salt gave the optically inactive bromide. However, in reference 28 it is reported that the bromide from silver (+)-2-ethylhexanoate had some optical activity.

TABLE I—*Continued*

FORMATION OF ALKYL HALIDES FROM ALIPHATIC MONOCARBOXYLIC ACIDS

Acid	Solvent	Main Product	Yield, %	Reference
n-$C_{11}H_{23}CO_2H$	CCl_4	n-$C_{11}H_{23}Br$	59–80	3, 54, 55
	CCl_4	n-$C_{11}H_{23}Br$	75–80	3
	$CHCl_3$	n-$C_{11}H_{23}I$	51–65	8
	Pet. ether	n-$C_{11}H_{23}I$	72–87	8
	C_6H_6	n-$C_{11}H_{23}I$	70–78	8
	CCl_4	n-$C_{11}H_{23}I$	66†	63
$(i$-$C_5H_{11})_2CHCO_2H$		$(i$-$C_5H_{11})_2CHBr$	65–77; 70	55, 58
n-$C_{13}H_{27}CO_2H$	CCl_4	n-$C_{13}H_{27}Br$	51	87
	CCl_4	n-$C_{13}H_{27}I$	18	87
n-$C_{15}H_{31}CO_2H$	CCl_4	n-$C_{15}H_{31}Cl$	30	87
	$C_2H_4Cl_2$	n-$C_{15}H_{31}Cl$	70–80	3, 55, 87
	CCl_4	n-$C_{15}H_{31}Br$	15–47	87
	CCl_4	n-$C_{15}H_{31}I$	Variable	3
n-$C_{17}H_{35}CO_2H$	None	n-$C_{17}H_{35}Cl$	73–86; 89†	55, 63
	CCl_4	n-$C_{17}H_{35}Br$	38 crude	20
	CCl_4	n-$C_{17}H_{35}Br$	60	87
	CCl_4	n-$C_{17}H_{35}I$	65	8
	C_6H_6	n-$C_{17}H_{35}I$		

† The yield is not based on pure isolated material, but on a quantitative determination of bromine present in the neutral fraction of the reaction mixture.

TABLE II

FORMATION OF ALKYL HALIDES FROM PHENYL-SUBSTITUTED CARBOXYLIC ACIDS
Unless otherwise indicated, the solvent was carbon tetrachloride.

Acid	Main Product	Yield, %	Reference
$C_6H_5CH_2CO_2H$	$C_6H_5CH_2Br$	54*	63
	$C_6H_5CH_2Br$	20–37†	25
$p\text{-}O_2NC_6H_4CH_2CO_2H$	$p\text{-}O_2NC_6H_4CH_2Br$	85	16
$(C_6H_5)_2CHCO_2H$	$(C_6H_5)_2CHBr$	8	25
$(C_6H_5)_3CCO_2H$	$(C_6H_5)_3COH$	8	25
$CH_3CH(C_6H_5)CO_2H$	$CH_3CHBrC_6H_5$	—‡	27
$C_6H_5CH_2CH_2CO_2H$	$C_6H_5CH_2CH_2Br$	5–15	16, 25
$p\text{-}O_2NC_6H_4CH_2CH_2CO_2H$	$p\text{-}O_2NC_6H_4CH_2CH_2Br$	80	16
$C_6H_5CH_2CH(C_6H_5)CO_2H$	$C_6H_5CHBrCHBrC_6H_5$	52	16
$(+)\text{-}C_6H_5CH_2CH(C_2H_5)CO_2H$	$(+,-)\text{-}C_6H_5CH_2CHBrC_2H_5$	17	26
$(-)\text{-}C_6H_5CH_2CH(C_2H_5)CO_2H$	$(+,-)\text{-}C_6H_5CH_2CHBrC_2H_5$	—	26
$C_6H_5C{\equiv}CCO_2H$§	$C_6H_5C{\equiv}CI$	94‖	49

* This yield is based on a quantitative determination of bromine present in the neutral fraction of the reaction mixture and not on pure isolated material.

† The silver salt was added to bromine in carbon tetrachloride, the reverse of the normal procedure.

‡ It was originally reported[27] that 1-bromo-1-phenylethane was obtained in 55% yield. Other chemists[83,85] could not obtain this product, and, in attempts to repeat their own work, the original workers have also reported failure;[28] no alkyl bromide was obtained.

§ Although no identifiable substances were isolated from the products resulting from the action of iodine on silver cinnamate or silver crotonate, silver phenyl-propiolate gave an excellent yield of the iodide. A small amount of triiodostyrene was formed simultaneously.

‖ The solvent used in this experiment was benzene.

TABLE III

FORMATION OF HALIDES AND/OR LACTONES FROM DICARBOXYLIC ACIDS
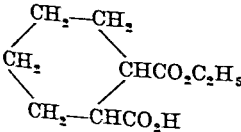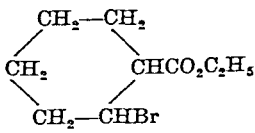
Unless otherwise indicated, the solvent was carbon tetrachloride.

Acid	Main Product	Yield, %	Reference
$HO_2C(CH_2)_2CO_2H$*	$Br(CH_2)_2Br$	32–37†	40, 85
$HO_2C(CH_2)_3CO_2H$	$\overline{OCCH_2CH_2CH_2O}$	69‡	63
$HO_2CCH(C_2H_5)CO_2H$*	$C_2H_5CHBr_2$§	28	40
$HO_2CCH_2CH(CH_3)CO_2H$	$BrCH_2CHBrCH_3$	12	63
$HO_2C(CH_2)_4CO_2H$	$Br(CH_2)_4Br$	Small	20
	$Br(CH_2)_4Br$	21	54
	$Br(CH_2)_4Br$*	58	84
	$Br(CH_2)_4Br$‖	28	63
$HO_2C(CH_2)_2CH(CH_3)CO_2H$	$\overline{OCCH_2CH_2CH(CH_3)O}$¶	87‡	63
$HO_2C(CH_2)_5CO_2H$	$Br(CH_2)_5Br$	44 ‡	63
$HO_2C(CH_2)_2C(CH_3)_2CO_2H$	$\overline{OCCH_2CH_2C(CH_3)_2O}$¶	50‡	63
$2\text{-}HO_2CC_6H_4CO_2H$	$2\text{-}BrC_6H_4Br$	10	63
$3\text{-}HO_2CC_6H_4CO_2H$	$3\text{-}BrC_6H_4Br$**	4	63
$4\text{-}HO_2CC_6H_4CO_2H$		—**	63
$HO_2C(CH_2)_7CO_2H$	$Br(CH_2)_7Br$	82‡	63
$HO_2CCH_2CH(C_5H_{11}\text{-}i)CO_2H$	$BrCH_2CHBrC_5H_{11}\text{-}i$	25‡	63
$HO_2C(CH_2)_8CO_2H$	$Br(CH_2)_8Br$	62–81	3, 54, 63
$HO_2C(CH_2)_2CH(C_5H_{11}\text{-}i)CO_2H$	$\overline{OCCH_2CH_2CH(C_5H_{11}\text{-}i)O}$¶	60‡	63
$HO_2CC(CH_2)_3CH(C_5H_{11}\text{-}i)CO_2H$	$Br(CH_2)_3CHBrC_5H_{11}\text{-}i$‖	33‡	63
$HO_2C(CH_2)_{10}CO_2H$	$Br(CH_2)_{10}Br$	60	3
$HO_2C(CH_2)_{14}CO_2H$	$Br(CH_2)_{14}Br$	44	54
$C_6H_5CH(CO_2H)CH(CO_2H)C_6H_5$	$C_6H_5CHBrCHBrC_6H_5$††	High	26
$HO_2C(CH_2)_3CH(CO_2H)CH_2CO_2H$*	$Br(CH_2)_3CHBrCH_2Br$	4–6	40

TABLE IV

FORMATION OF HALO ESTERS FROM ACID ESTERS

Unless otherwise indicated, the solvent was carbon tetrachloride.

Silver Salt of Acid	Main Product	Yield, %	Reference
$CH_3O_2C(CH_2)_4CO_2H$	$CH_3O_2C(CH_2)_4Br$	65–68	4, 60, 61
$CH_3O_2C(CH_2)_6CO_2H$	$CH_3O_2C(CH_2)_6Br$	70	4
$CH_3O_2C(CH_2)_7CO_2H$	$CH_3O_2C(CH_2)_7Br$	70	4
$CH_3O_2C(CH_2)_8CO_2H$	$CH_3O_2C(CH_2)_8Br$	75	3, 4
$CH_3O_2C(CH_2)_9CO_2H$	$CH_3O_2C(CH_2)_9Br$	71	3, 4
$CH_3O_2C(CH_2)_{11}CO_2H$	$CH_3O_2C(CH_2)_{11}Br$	78	4
$CH_3O_2C(CH_2)_{12}CO_2H$	$CH_3O_2C(CH_2)_{12}Br$	71	4
$CH_3O_2C(CH_2)_{13}CO_2H$	$CH_3O_2C(CH_2)_{13}Br$	73	4
$CH_3O_2C(CH_2)_{14}CO_2H$	$CH_3O_2C(CH_2)_{14}Br$	70 (65–70)	4, 62
	$CH_3O_2C(CH_2)_{14}Br$	78–85*	62
$CH_3O_2C(CH_2)_{15}CO_2H$	$CH_3O_2C(CH_2)_{15}Br$	70	4
$CH_3O_2C(CH_2)_{16}CO_2H$	$CH_3O_2C(CH_2)_{16}Br$	75	4

$$\begin{matrix} CH_2\!-\!CH_2 & & \\ CH_2 \qquad CHCO_2C_2H_5 & & \\ CH_2\!-\!CHCO_2H & & \end{matrix} \qquad \begin{matrix} CH_2\!-\!CH_2 & & \\ CH_2 \qquad CHCO_2C_2H_5 & \quad 68\text{–}72 & \quad 5 \\ CH_2\!-\!CHBr & & \end{matrix}$$

* The solvent in this experiment was trichloroethylene.

TABLE V

FORMATION OF ALKYL HALIDES FROM POLYHALO AND PERFLUORO ACIDS*

Acid	Product	Yield, %	Reference
CH_2FCO_2H	CH_2FCl	52	73
	CH_2FBr	62	73
	CH_2FI	55	73
$CHFClCO_2H$	$CHFCl_2$	73	73
	$CHFClBr$	67	73
	$CHFClI$	35	73
$CHFBrCO_2H$	$CHFBrCl$	67	73
	$CHFBr_2$	64	73
	$CHFBrI$	19	73
$CHFICO_2H$	$CHFI_2$	18	73
CHF_2CO_2H	CHF_2Cl	91	73
	CHF_2Br	88–93	73
	CHF_2I	93	73
$CFClBrCO_2H$	$CFCl_2Br$	63	73
	$CFClBr_2$	71	73
$CFCl_2CO_2H$ } mixture $CHFClCO_2H$ }	$CFCl_3$	63	73
	$CHFCl_2$	78	73
	$CFCl_2Br$	58	73
	$CHFClBr$	61	73
	$CFCl_2I$	10	73
	$CHFClI$	29	73
CF_2BrCO_2H	CF_2Br_2	81	73
CF_2ClCO_2H	CF_2Cl_2	88	73
	CF_2ClBr	91	73
	CF_2ClI	78	73
CCl_3CO_2H	—	—	49

* Unless otherwise specified, the reactions with chlorine and bromine were carried out in sealed tubes or in a steel autoclave without a solvent; with iodine an intimate mixture of the halogen and silver salt was heated in an open flask.

TABLE V—*Continued*
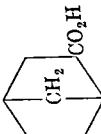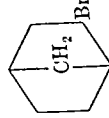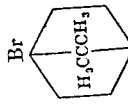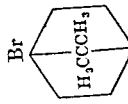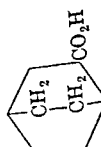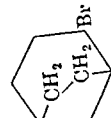
FORMATION OF ALKYL HALIDES FROM POLYHALO AND PERFLUORO ACIDS
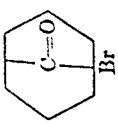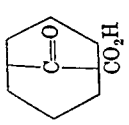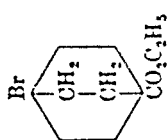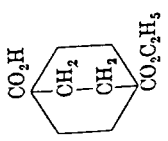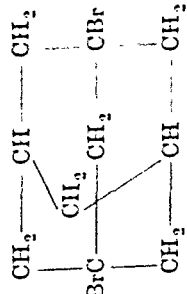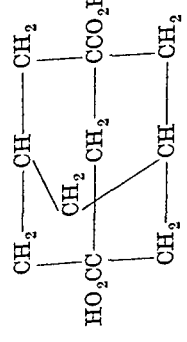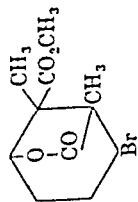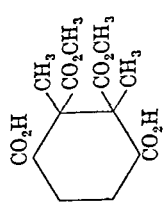
Acid	Product	Yield, %	Reference
CF_3CO_2H	CF_3Cl	90; 88	78, 79
	CF_3Br	88; 98	78, 79
	CF_3I	87–95	74, 77, 78
$C_2F_5CO_2H$	C_2F_5Cl	94; 83	73, 79
	C_2F_5Br	98; 98	73, 79
	C_2F_5I	94; 86	73, 74
$n\text{-}C_3F_7CO_2H$	$n\text{-}C_3F_7Cl$	91; 71	73, 79
	$n\text{-}C_3F_7Br$	97; 95	73, 79
	$n\text{-}C_3F_7I$	90; 86–93	73, 74, 80
$n\text{-}C_4F_9CO_2H$	$n\text{-}C_4F_9Cl$	89	73
	$n\text{-}C_4F_9Br$	95	73
	$n\text{-}C_4F_9I$	89	73
$n\text{-}C_5F_{11}CO_2H$	$n\text{-}C_5F_{11}Cl$	85; 71	73, 75
	$n\text{-}C_5F_{11}Br$	91; 83	73, 75
	$n\text{-}C_5F_{11}I$	89; 74	73, 75
$n\text{-}C_6F_{13}CO_2H$	$n\text{-}C_6F_{13}Cl$	83	73
	$n\text{-}C_6F_{13}Br$	90	73
	$n\text{-}C_6F_{13}I$	90	73
$n\text{-}C_7F_{15}CO_2H$	$n\text{-}C_7F_{15}Cl$	80	73
	$n\text{-}C_7F_{15}Br$	86	73
	$n\text{-}C_7F_{15}I$	85	73
$HO_2C(CF_2)_3CO_2H$	$Cl(CF_2)_3Cl$	64	86
	$Br(CF_2)_3Br$	80	86
	$I(CF_2)_3I$	18†	74, 86
$\begin{array}{c} CF_2\!-\!CF_2 \\ CF_2 \qquad CFCO_2H \\ CF_2\!-\!CF_2 \end{array}$	$C_6F_{11}Br‡$	54	76
	$C_6F_{11}I‡$	63	76

† The main product of the reaction is perfluorobutyrolactone.
‡ Perfluorotributylamine was used as a solvent.

TABLE VI

FORMATION OF ALICYCLIC BROMIDES FROM ALICYCLIC CARBOXYLIC ACIDS

Acid	Solvent	Main Product	Yield, %	Reference
$CH_2(CH_2)_2CHCO_2H$	$C_2H_4Cl_2$	CH_2CH_2CHBr*	15–20	67
	CCl_2F_2	CH_2CH_2CHBr	53	67
$CH_2(CH_2)_2CHCO_2H$	CCl_4, CF_2Cl_2	$CH_2(CH_2)_2CHBr$*†	50, 57	35, 48
$CH_2(CH_2)_3CHCO_2H$	CCl_4	$CH_2(CH_2)_3CHBr$	73–80	5
$CH_2(CH_2)_4CHCO_2H$	CCl_4	$CH_2(CH_2)_4CHCl$	70	5
	CCl_4	$CH_2(CH_2)_4CHBr$	73–80; 57	5, 63
$CH_2(CH_2)_5CHCO_2H$	CCl_4	$CH_2(CH_2)_5CHBr$	80	5
(cyclohexane)–CH_2CO_2H	CCl_4	(cyclohexane)–CH_2Br	55	69
(cyclohexane)–CO_2H	Pet. ether	(cyclohexane)–Br	50+	37
(cyclohexane, H_3CCCH_3)–CO_2H	CCl_4 (high temp.)	(cyclohexane, H_3CCCH_3)–Br	58+	37
	CCl_4 (low temp.)		60+	37
(cyclohexane)–$CH_2CH_2CO_2H$	—	(cyclohexane)–CH_2CH_2Br	—	68, 69

71

88

70

72

74

55

28

—

CCl₄

CCl₂F₂

CCl₄

* The silver salt was added to the bromine in the solvent at −25 to −35°, the reverse of the normal addition.
† This reaction has also been run with the mercuric salt. See Table IX.
‡ The products are mixtures of chloro- and bromo-apocamphane. Attempts at separation failed.

TABLE VII

FORMATION OF ARYL HALIDES FROM AROMATIC CARBOXYLIC ACIDS*

Substituents in Aromatic Acid (Benzoic)	Substituents in Aryl Bromide (Bromobenzene)	Yield, %	Reference
None	None	14–18	16, 20
None	None	46–80	17, 20, 63
2-Chloro	2-Chloro	38	16
		46	17
3-Chloro	3-Chloro	44	16
4-Chloro	4-Chloro	55	16
2-Nitro	2-Nitro	95, 71	16, 63
3-Nitro	3-Nitro	89	16
		68	17
4-Nitro	4-Nitro	79	16
3-Methyl	3-Methyl†	27	17
4-Methyl	4-Methyl‡	17	16
3-Methoxy	2-Carboxy-4-methoxy	50	17
4-Methoxy	3-Bromo-4-methoxy§	19–23	16
3-Bromo-4-methoxy	3-Bromo-4-methoxy	92	16

* In all the reactions recorded in this table carbon tetrachloride was used as the solvent.
† 3,4-Dibromotoluene was also obtained in 13% yield.
‡ The principal product was 3-bromo-*p*-toluic acid, obtained in 66% yield.
§ The principal product was 3-bromo-4-methoxybenzoic acid, obtained in 73% yield.

TABLE VIII

FORMATION OF SUBSTITUTED ALKYL HALIDES OR THEIR DECOMPOSITION PRODUCTS FROM SUBSTITUTED MONOCARBOXYLIC ACIDS

Acid	Solvent	Product	Yield, %	Reference
A. Hydroxy Acids				
$C_6H_5CHOHCO_2H$	$(C_2H_5)_2O$	C_6H_5CHO	Variable	3
$n\text{-}C_{14}H_{29}CHOHCO_2H$	None	$n\text{-}C_{14}H_{29}CHO$	—	3
B. Halogen Acids				
$BrCH_2CH_2CO_2H$*	CCl_4	$Br(CH_2)_2Br$	69	40
$CH_3(CH_2)_2CHBrCO_2H$*	CCl_4	$CH_3(CH_2)_2CHBr_2$	52	40
$n\text{-}C_{16}H_{33}CHBrCO_2H$	CCl_4	$n\text{-}C_{16}H_{33}CHBr_2$	70–75 crude	3
$n\text{-}C_8H_{17}(CHCl)_2(CH_2)_7CO_2H$	CCl_4	$n\text{-}C_8H_{17}(CHCl)_2(CH_2)_7Br$	76 crude	3
$n\text{-}C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7CO_2H$*	CCl_4	$n\text{-}C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7Br$	—	59
C. Keto Acids				
CH_3COCO_2H	CCl_4	CH_3COBr	—	3
$CH_3CO(CH_2)_7CO_2H$	CCl_4	$CH_3CO(CH_2)_7Br$	39†	63
D. Amino Acids‡				
$CH_3CH(NHCOC_6H_5)CO_2H$	CH_3CO_2H	$CH_3CH(NHCOC_6H_5)Br$	Variable	81
$n\text{-}C_4H_9CH(NHCOCH_3)CO_2H$	$(C_2H_5)_2O$	$n\text{-}C_4H_9CH(NHCOCH_3)Br$	Variable	81
$n\text{-}C_4H_9CH(NHCOC_6H_5)CO_2H$	CCl_4	$n\text{-}C_4H_9CH(NHCOC_6H_5)Br$	Variable	81
$C_6H_5CH_2CH(NHCOC_6H_5)CO_2H$	CH_3CO_2H	$C_6H_5CH_2CH(NHCOC_6H_5)Br$	Variable	81

* The dry silver salt was added to the halogen in carbon tetrachloride at a low temperature.

† The yield is not based on isolated material, but on a quantitative determination of the halogen present in the neutral fraction of the reaction mixture.

‡ The substituted alkyl halides formed from acylated amino acids are highly hygroscopic materials which decompose in water with the formation of aldehyde, amide, and hydrogen bromide. The yields of aldehyde isolated through the dinitro-phenylhydrazone are variable (20–45%).

TABLE VIII—*Continued*

FORMATION OF SUBSTITUTED ALKYL HALIDES OR THEIR DECOMPOSITION PRODUCTS FROM SUBSTITUTED MONOCARBOXYLIC ACIDS

E. Alicyclic Acetic Acid

$CH_3CH_2CH_2CH_2CHClCH_2CO_2H$ $\xrightarrow{CCl_4}$ $CH_3CH_2CH_2CH_2CHCH_2Br$ 67–73   5

F. Bile Acids

Steroid skeleton with ring positions labeled 1, 3, 5, 7, 12, 17; angular CH_3 groups; side-chain substituents R', R'' (and CH_3, R'' at C-17 side chain).

Substituents in Acid				Solvent	Substituents in Product				Yield, %	Reference
R =	R' =	R'' =	R''' =		R =	R' =	R'' =	R''' =		
CH_3CO_2	H	H	CO_2H	C_2H_5Br	CH_3CO_2	H	H	Br	Very poor	65
CH_3CO_2	H	CH_3CO_2	$CH(CH_3)CO_2H$	CCl_4	CH_3CO_2	H	CH_3CO_2	$CH(CH_3)Br$	65	64
CH_3CO_2	H	CH_3CO_2	$CH(CH_3)CH_2CO_2H$	CCl_4	CH_3CO_2	H	CH_3CO_2	$CH(CH_3)CH_2Br$	40	64
H	H	H	$CH(CH_3)CH_2CH_2CO_2H$	C_2H_5Br	H	H	H	$CH(CH_3)CH_2CH_2Br$	89	65a
CH_3CO_2	H	H	$CH(CH_3)CH_2CH_2CO_2H$	C_2H_5Br	CH_3CO_2	H	H	$CH(CH_3)CH_2CH_2Br$	60	65a
H	H	O	$CH(CH_3)CH_2CH_2CO_2H$	CCl_4	H	H	O	$CH(CH_3)CH_2CH_2Br$	60	64
CH_3CO_2	H	O	$CH(CH_3)CH_2CH_2CO_2H$	CCl_4	CH_3CO_2	H	O	$CH(CH_3)CH_2CH_2Br$	25	64
CH_3CO_2	H	CH_3CO_2	$CH(CH_3)CH_2CH_2CO_2H$	CCl_4	CH_3CO_2	H	CH_3CO_2	$CH(CH_3)CH_2CH_2Br$	—	65a
CH_3CO_2	CH_3CO_2	H	$CH(CH_3)CH_2CH_2CO_2H$	C_2H_5Br	CH_3CO_2	CH_3CO_2	H	$CH(CH_3)CH_2CH_2Br$	Poor	65
CH_3CO_2	CH_3CO_2	CH_3CO_2	$CH(CH_3)CH_2CH_2CO_2H$	C_2H_5Br	CH_3CO_2	CH_3CO_2	{2OH, 1CH_3CO_2}	$CH(CH_3)CH_2CH_2Br$	—§	65a

§ The product was amorphous.

TABLE IX

FORMATION OF HALOGEN COMPOUNDS BY THE ACTION OF HALOGEN ON VARIOUS METALLIC SALTS OF CARBOXYLIC ACIDS

Acid	Salt	Solvent	Product	Yield, %	Reference
$HOCH_2CO_2H$	Hg^{++}	CS_2	CH_2O	60–80	3
CF_3CO_2H	Na^*	None	CF_3I	58–61	78
	K^*	None	CF_3I	40	73, 78
	Ba^*	None	CF_3I	32	78
	Hg^{+++*}	None	CF_3I	35	78
	Pb^*	None	CF_3I	26	73, 78
$CH_2(CH_2)_2CHCO_2H$	Hg^{++}	CS_2	$CH_2(CH_2)_2CHBr$	45	5
$C_2H_5O_2CCH_2CO_2H$	K	CCl_4	$C_2H_5O_2CCH_2Br$	23	82
$n\text{-}C_6H_{13}CO_2H$	Tl^+	CCl_4	$n\text{-}C_6H_{13}Cl$	High	3
$n\text{-}C_6H_{13}CO_2H$	Tl^+	CCl_4	$n\text{-}C_6H_{13}Br$	100	3
$C_2H_5O_2CCH(C_2H_5)CO_2H$	K	CCl_4	$C_2H_5O_2CCHClC_2H_5$	41	83
	K	CCl_4	$C_2H_5O_2CCHBrC_2H_5$	36	82
$n\text{-}C_7H_{15}CO_2H$	K	CCl_4	$n\text{-}C_7H_{15}Br$	45	4
	Hg^+	CCl_4	$n\text{-}C_7H_{15}Br$	60	3
	Hg^+	CS_2	$n\text{-}C_7H_{15}Br$	75	3, 4
$C_2H_5O_2CCH(C_3H_7\text{-}i)CO_2H$	K	CCl_4	$C_2H_5O_2CCHBrC_3H_7\text{-}i$	30	82
$C_2H_5O_2CCH(C_4H_9\text{-}n)CO_2H$	K	CCl_4	$C_2H_5O_2CCHClC_4H_9\text{-}n$	52	83
	K	CCl_4	$C_2H_5O_2CCHBrC_4H_9\text{-}n$	67	82
$C_2H_5O_2CCH(C_6H_{13}\text{-}n)CO_2H$	K	CCl_4	$C_2H_5O_2CCHClC_6H_{13}\text{-}n$	54	83
$C_2H_5O_2CCH(C_6H_{11})CO_2H$	K	CCl_4	$C_2H_5O_2CCHBrC_6H_{11}$	45	82
$C_2H_5O_2CCH(CH_2C_6H_5)CO_2H$	K	CCl_4	$C_2H_5O_2CCHBrCH_2C_6H_5$	80	82
$C_2H_5O_2CCH(C_8H_{17}\text{-}n)CO_2H$	K	CCl_4	$C_2H_5O_2CCHClC_8H_{17}\text{-}n$	20	83
$C_2H_5O_2CCH(C_{10}H_{21}\text{-}n)CO_2H$	K	CCl_4	$C_2H_5O_2CCHClC_{10}H_{21}\text{-}n$	16	83
$n\text{-}C_{15}H_{31}CO_2H$	Hg^{++}	CCl_4	$n\text{-}C_{15}H_{31}Br$	60–70	3

* The reaction was carried out in a steel autoclave at 270°.

TABLE XI

FORMATION OF ALDEHYDES AND KETONES BY THE ACTION OF
IODINE ON THE SILVER SALTS OF HYDROXY ACIDS

Acid	Diluent	Product	Yield, %	Reference
$HOCH_2CO_2H$	C_2H_5OH	CH_2O*	—	49, 89
$CH_2OHCHOHCO_2H$	Quartz	CH_2O*	—	89
$CH_3CHOHCO_2H$	C_2H_5OH	CH_3CHO*	—	49, 89
$C_6H_5CHOHCO_2H$	$(C_2H_5)_2O$	C_6H_5CHO	60†	49, 89
$(CH_3)_2C(OH)CO_2H$	C_2H_5OH	$(CH_3)_2CO$*	—	89
$(C_6H_5)_2C(OH)CO_2H$	C_6H_6	$C_6H_5COC_6H_5$*	—	49

* This material was identified as one product of the reaction mixture; no yields were recorded.

† The product was contaminated with benzene which was the solvent used in one case.[49]

		Product	Diluent	Starting material		
26	49, 92	CH$_2$—CH$_2$, CH—CO, O, CH$_2$ / CH$_2$, CH$_2$—CH	Sand	CH$_2$—CH$_2$, CHCO$_2$H (cis)* / CH$_2$, CH$_2$—CHCH$_2$CO$_2$H		
—	92	CH$_2$—CH$_2$, CH$_2$CO, C, CH$_2$O / CH$_2$, CH$_2$—CH$_2$	None	CH$_2$—CH$_2$, C(CH$_2$CO$_2$H)$_2$ / CH$_2$, CH$_2$—CH$_2$		
—	92	CH—CO, O, H$_3$CCCH$_3$, C, CH$_3$ / CH$_2$, CH$_2$	Sand	CH$_2$—CHCO$_2$H, H$_3$CCCH$_3$, CO$_2$H / CH$_2$, CH$_3$		
16	93	CH$_2$—CH$_2$, CH$_2$CO, C, CH$_2$O / H$_3$CCH, CH$_2$—CH$_2$	None	CH$_2$—CH$_2$, C(CH$_2$CO$_2$H)$_2$ / H$_3$CCH, CH$_2$—CH$_2$		

* The *trans*-isomer also gave the *cis*-lactone, but in a smaller yield.

TABLE XIII

ADDITION OF ACYL HYPOHALITES TO OLEFINS

The acyl hypohalite was prepared from the silver salt of the acid and halogen and was used without isolation. Exceptions to this statement are indicated by footnotes.

Olefin	Acyl Hypohalite	Solvent	Product	Yield, %	Reference
Ethylene	$C_6H_5CO_2I$	C_6H_6	Ethanediol dibenzoate	Good	10
	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$*	$(C_2H_5)_2O$	2-Iodoethyl 3,5-dinitrobenzoate	—	96
Propene	$C_6H_5CO_2I$	C_6H_6	1,2-Propanediol dibenzoate	Good	10
	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	1-Iodo-2-propyl 3,5-dinitrobenzoate	—	96
Allyl chloride	CH_3CO_2Cl	CCl_4	2,3-Dichloropropyl acetate	48	20
Allyl bromide	CH_3CO_2Br	CCl_4	2,3-Dibromopropyl acetate	85	97
	$C_3H_7CO_2Br$	CCl_4	2,3-Dibromopropyl butyrate	—	97
	$C_6H_5CO_2Br$	CCl_4	2,3-Dibromopropyl benzoate	—	97
1-Butene	$3,5\text{-}(NO_2)_2C_6H_3CO_2Cl$	$CHCl_3$	1-Chloro-2-butyl 3,5-dinitrobenzoate	—	96
	$3,5\text{-}(NO_2)_2C_6H_3CO_2Br$	$CHCl_3$	1-Bromo-2-butyl 3,5-dinitrobenzoate	—	96
	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	1-Iodo-2-butyl 3,5-dinitrobenzoate	—	96
cis-2-Butene	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	threo-3-Iodo-2-butyl 3,5-dinitrobenzoate	—	96
trans-2-Butene	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	erythro-3-Iodo-2-butyl 3,5-dinitrobenzoate	—	96
Isobutene	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	1-Iodo-2-methyl-2-propyl 3,5-dinitrobenzoate	—	96

Substrate	Reagent	Solvent	Product	Yield (%)	References
Butadiene	$C_6H_5CO_2I\dagger$	C_6H_6	1,2,3,4-Butanotetrol tetrabenzoate	60	11
	$C_6H_5CO_2I\ddagger$	C_6H_6	1-Butene-3,4-diol	80	11
			2-Butene-1,4-diol	4	
1-Pentene	CH_3CO_2I	C_6H_6	1,2-Pentanediol diacetate	Good	10
	$C_6H_5CO_2I$	C_6H_6	1,2-Pentanediol dibenzoate	Good	10
	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	1-Iodo-2-pentyl 3,5-dinitro-benzoate	—	96
Cyclopentene	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	2-Iodocyclopentyl 3,5-dinitro-benzoate	—	96
1-Hexene	$3,5\text{-}(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	1-Iodo-2-hexyl 3,5-dinitro-benzoate	—	96
Cyclohexene	CH_3CO_2Br	CCl_4	2-Bromocyclohexyl acetate	32	22
	$CH_3CO_2I\S$	$(C_2H_5)_2O$	2-Iodocyclohexyl acetate	80	21, 94
	$C_2H_5CO_2Br$	$CHCl_3;\ C_5H_5N$	2-Bromocyclohexyl propionate	48	22
	$n\text{-}C_3H_7CO_2Br$	$CHCl_3 + C_5H_5N$	2-Bromocyclohexyl n-butyrate	47	22
		CCl_4	2-Bromocyclohexyl n-butyrate‖	50	20
	$C_6H_5CO_2Cl$	CCl_4	2-Chlorocyclohexyl benzoate	Good	14, 22
	$C_2H_5CO_2Br$	CCl_4	2-Bromocyclohexyl benzoate	40–42	20, 22
		CCl_4	2-Bromocyclohexyl benzoate	Good	14
	$C_6H_5CO_2I$	$(C_2H_5)_2O;\ CCl_4$	2-Iodocyclohexyl benzoate	60	14, 21
		C_6H_6	(+, −)-trans-1,2-Cyclohexanediol dibenzoate	44	101

* This reagent was used to identify olefins;[96] no yields were recorded though they are presumably high.

† A large excess of the complex and additional silver benzoate were employed.

‡ A limited quantity of the complex was employed.

§ Mercuric rather than silver acetate was used.

‖ Some dibromocyclohexane was formed simultaneously.

TABLE XIII—*Continued*

Olefin	Acyl Hypohalite	Solvent	Product	Yield, %	Reference
Cyclohexene (*Contd.*)					
	m-$NO_2C_6H_4CO_2Br$	CCl_4	2-Bromocyclohexyl m-nitrobenzoate	44	22
	$3,5$-$(NO_2)_2C_6H_3CO_2Br$	C_6H_6	$(+,-)$-*trans*-2-Bromocyclohexyl 3,5-dinitrobenzoate	27	101
		C_6H_6	$(+,-)$-*trans*-1,2-Cyclohexanediol bis-3,5-dinitrobenzoate	10	101
	$3,5$-$(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	2-Iodocyclohexyl 3,5-dinitrobenzoate	—	96
	CO_3I_2	$(C_2H_5)_2O$	Di-2-iodocyclohexyl carbonate	80	95
	IO_2CCO_2I	$(C_2H_5)_2O$	Di-2-iodocyclohexyl oxalate	—	95
	$IO_2C(CH_2)_2CO_2I$	$(C_2H_5)_2O$	Di-2-iodocyclohexyl succinate	50	95
	o-$C_6H_4(CO_2I)_2$	$(C_2H_5)_2O$	Di-2-iodocyclohexyl phthalate	60	95
		C_6H_6	1,2,5,6-Hexanetetrol tetrabenzoate	—	10
1,5-Hexadiene	$C_3H_5CO_2Br$	C_6H_6	Syrup; mixture of diacetates	—	10, 11
2,4-Hexadiene	CH_3CO_2I	C_6H_6	$+,-)$-*trans*-4,5-Cyclohexenediol dibenzoate	37	101
1,4-Cyclohexadiene	$C_6H_5CO_2Br$	C_6H_6	(1,4)R-1,2,4,5-Cyclohexanetetrol tetrabenzoate	11	101
1-Heptene	$3,5$-$(NO_2)_2C_6H_3CO_2I$	$(C_2H_5)_2O$	1-Iodo-2-heptyl 3,5-dinitrobenzoate	—	96
Styrene	CH_3CO_2Br	CCl_4	2-Bromo-1-phenylethyl acetate	60	51
	$C_6H_5CO_2I$	C_6H_6	Phenylethanediol dibenzoate	Good	10
	$(+)$-$C_4H_9CH(C_2H_5)CO_2Br$	CCl_4	$(+)$-2-Bromo-1-phenylethyl 2-ethylhexanoato	60	51

TABLE XIV

NUCLEAR HALOGENATION WITHOUT DECARBOXYLATION BY THE ACTION OF HALOGEN ON SILVER SALTS OF ACIDS

Acid	Solvent	Product	Yield, %	Reference
$C_6H_5CO_2H$	—	$3\text{-}BrC_6H_4CO_2H$	—	102
	—	$3\text{-}IC_6H_4CO_2H$	—	15
$2\text{-}HOC_6H_4CO_2H$	—	$?\text{-}I_2\text{-}2\text{-}HOC_6H_2CO_2H$	—	15
$3\text{-}CH_3OC_6H_4CO_2H$	CCl_4	$2\text{-}Br\text{-}5\text{-}CH_3OC_6H_3CO_2H$	50	17
$4\text{-}CH_3OC_6H_4CO_2H$	CCl_4	$3\text{-}Br\text{-}4\text{-}CH_3OC_6H_3CO_2H$	73-78	16
$4\text{-}CH_3C_6H_4CO_2H$	CCl_4	$3\text{-}Br\text{-}4\text{-}CH_3C_6H_3CO_2H$	66	16
$3\text{-}CH_3OC_6H_4(CH_2)_2CO_2H$	CCl_4	$2\text{-}Br\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$	88	18
	CCl_4	$2\text{-}I\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$	90	18
$4\text{-}CH_3OC_6H_4(CH_2)_4CO_2H$	CCl_4	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_4CO_2H$	84	18

TABLE XV

NUCLEAR HALOGENATION OF AROMATIC SUBSTANCES BY THE ACTION OF SILVER ACETATE AND HALOGEN

Aromatic Substance	Solvent	Product	Yield, %	Reference
$CH_3OC_6H_5$	CCl_4	$4\text{-}BrC_6H_4OCH_3$	20	17
$4\text{-}CH_3OC_6H_4CH_2CO_2H$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3CH_2CO_2H$	82	18
$3\text{-}CH_3OC_6H_4(CH_2)_2CO_2H$	CH_3CO_2H	$2\text{-}Br\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$	82	18
	CH_3CO_2H	$2\text{-}I\text{-}5\text{-}CH_3OC_6H_3(CH_2)_2CO_2H$	84	18
$4\text{-}CH_3OC_6H_4(CH_2)_3CO_2H$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_3CO_2H$	86	18
$4\text{-}C_2H_5OC_6H_4(CH_2)_3CO_2H$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}C_2H_5OC_6H_3(CH_2)_3CO_2H$	80	18
$3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_3CO_2H$	CH_3CO_2H	$?\text{-}I\text{-}3,4(CH_3O)_2C_6H_2(CH_2)_3CO_2H$	81	18
$4\text{-}CH_3OC_6H_4(CH_2)_4CO_2H$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_4CO_2H$	80	18
$4\text{-}CH_3OC_6H_4(CH_2)_5CO_2H$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_5CO_2H$	84	18
$4\text{-}CH_3OC_6H_4(CH_2)_9CO_2H$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_9CO_2H$	76	18
$3\text{-}CH_3\text{-}4\text{-}CH_3OC_6H_3(CH_2)_3CO_2C_2H_5$	CH_3CO_2H	$3\text{-}I\text{-}5\ CH_3\text{-}4\text{-}CH_3OC_6H_2(CH_2)_3CO_2C_2H_5$	74	18
$4\text{-}CH_3OC_6H_4(CH_2)_5CO_2C_2H_5$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_5CO_2C_2H_5$	88	18
$2,5\text{-}(CH_3)_2C_6H_3(CH_2)_9CO_2C_2H_5$	CH_3CO_2H	$4\text{-}I\text{-}2,5\text{-}(CH_3)_2C_6H_2(CH_2)_9CO_2C_2H_5$	56	18
$4\text{-}CH_3OC_6H_4(CH_2)_9CO_2C_2H_5$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}CH_3OC_6H_3(CH_2)_9CO_2C_2H_5$	76	18
$4\text{-}C_2H_5OC_6H_4(CH_2)_9CO_2C_2H_5$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}C_2H_5OC_6H_3(CH_2)_9CO_2C_2H_5$	78	18
$4\text{-}C_2H_5OC_6H_4(CH_2)_{10}CO_2C_2H_5$	CH_3CO_2H	$3\text{-}I\text{-}4\text{-}C_2H_5OC_6H_3(CH_2)_{10}CO_2C_2H_5$	60	18

TABLE XVI

NUCLEAR HALOGENATION OF AROMATIC SUBSTANCES BY THE ACTION OF SILVER TRIFLUOROACETATE AND HALOGEN

Aromatic Substance	Solvent	Product	Yield, %	Reference
C_6H_6	None	C_6H_5Br	89	19
	None	C_6H_5I*	85	19
$C_6H_5CH_3$	CCl_4	$4\text{-}BrC_6H_4CH_3$	73	52
	None	$4\text{-}BrC_6H_4CH_3$	90	19
	CCl_4	$4\text{-}IC_6H_4CH_3$	84	52
	None	$4\text{-}IC_6H_4CH_3$	88	19
C_6H_5Cl	None	$4\text{-}BrC_6H_4Cl$†	58	19
	None	$4\text{-}IC_6H_4Cl$†	62	19
C_6H_5Br	None	$4\text{-}BrC_6H_4Br$†	65	19
	None	$4\text{-}IC_6H_4Br$	71	19
C_6H_5I	None	$4\text{-}BrC_6H_4I$	85	19
	None	$4\text{-}IC_6H_4I$	77	19
$C_6H_5OCH_3$	None	$4\text{-}BrC_6H_4OCH_3$	76	19
	None	$4\text{-}IC_6H_4OCH_3$	75	19
$C_6H_4(OCH_3)_2\text{-}o$	None	4-Iodoveratrole	85	53a
$C_6H_5NH_2$	$CHCl_3$	$4\text{-}BrC_6H_4NH_2$	62	19
	None	$4\text{-}IC_6H_4NH_2$	51	19
$C_6H_5N(CH_3)_2$	None	$4\text{-}IC_6H_4N(CH_3)_2$	41	19
$C_6H_5NO_2$	None	$3\text{-}BrC_6H_4NO_2$‡	19	19
	None	CF_3I§	75	19
$C_6H_5CO_2H$	$C_6H_5NO_2$	$3\text{-}BrC_6H_4CO_2H$	61	19
	$C_6H_5NO_2$	$3\text{-}IC_6H_4CO_2H$∥	84	19
2-Methylnaphthalene	$(C_2H_5)_2O$	1-Bromo-2-methylnaphthalene	60	52
Thiophene	None	2,5-Diiodothiophene	—	19

* Six per cent of diiodobenzene was also formed.
† The infrared absorption indicates the presence of ortho derivative.
‡ Twenty-one per cent of CF_3Br was also formed.
§ No 3-iodonitrobenzene was formed.
∥ The infrared absorption shows no ortho or para derivative.

TABLE XVII

FORMATION OF HALOACETYLENES BY THE ACTION OF SILVER
BENZOATE AND HALOGEN ON ACETYLENES

Acetylene	Acylhypohalite (or Simonini Complex)	Solvent	Product	Yield	Reference
$HC\equiv CH$	$(C_6H_5CO_2)_2AgI$	C_6H_6	$HC\equiv CI$	—	12
	$2(C_6H_5CO_2)_2AgI$	C_6H_6	$IC\equiv CI$	—	12
$n\text{-}C_5H_{11}C\equiv CH$	$C_6H_5CO_2Cl$	CCl_4	$C_5H_{11}C\equiv CCl$	Good	14
	$C_6H_5CO_2Br$	CCl_4	$C_5H_{11}C\equiv CBr$	Good	14
	$C_6H_5CO_2I$	CCl_4	$C_5H_{11}C\equiv CI$	Good	14
$C_6H_5C\equiv CH$	$(C_6H_5CO_2)_2AgI$	C_6H_6	$C_6H_5C\equiv CI$	Quant.	12

CHAPTER 6

THE SYNTHESIS OF β-LACTAMS

JOHN C. SHEEHAN

Massachusetts Institute of Technology

AND

ELIAS J. COREY

University of Illinois

CONTENTS

INTRODUCTION

The four-membered ring appears to be the smallest cyclic system that is capable of accommodating the amide function as a constituent. Such four-membered, cyclic amides (I), commonly referred to as β-lactams,[1] possess physical and chemical properties that diverge sharply, partially

I
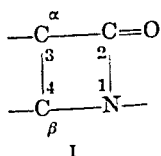
as a result of ring strain, from those of acyclic amides and lactams of greater ring size. Thus, in common with β-lactones and cyclobutanone derivatives, the simple β-lactams are unusually susceptible to reactions involving the carbonyl group and generally undergo facile ring cleavage. In addition, each of these small-ring systems presents considerable difficulty in synthesis. The reluctance with which β-lactams are formed, using the conventional methods of lactam synthesis, has necessitated the development of special and unique approaches to these compounds.

No authentic β-lactams were known until the beginning of the present century, probably because their synthesis by the method commonly used for γ-lactam formation, i.e. thermal dehydration of the appropriate amino acids, had not been realized. The first β-lactams were prepared by Staudinger and his co-workers,[2] using two highly novel methods which were discovered in connection with their studies on the chemistry of ketenes. During the twenty-odd years between the completion of Staudinger's work and 1943, two additional syntheses of β-lactams were discovered, and thereafter several more.

After 1943 interest in the synthesis and chemistry of β-lactams was stimulated by the importance of the natural penicillins and the problem of their structure and synthesis. When it became apparent that the natural penicillins might possess the β-lactam ring as a key feature, intensive studies were made of β-lactams, especially those possibly related

---

[1] β-Lactams may also be named as keto derivatives of the parent saturated heterocycle azetidine, i.e. as 2-azetidinones. This system of nomenclature has been used widely, cf. C.A., 38, 7061 (1944), and will be followed here in the naming of monocyclic β-lactams.

[2] Staudinger, Die Ketene, F. Enke, Stuttgart, 1912.

to the penicillins.   Early evidence in favor of the now accepted β-lactam-thiazolidine structure for the penicillins came from the investigation of the infrared absorption of the penicillins (II) and model β-lactams such as III.

RCONHCH—CH   C(CH$_3$)$_2$
　　　　　｜　　｜　　｜
　　　　　CO—N——CHCO$_2$H
　　　　　　　　II

(C$_6$H$_5$)$_2$C——C   CH$_2$
　　　　　｜　　｜　　｜
　　　　　CO—N——CH$_2$
　　　　　　　　III

After the β-lactam-thiazolidine formulation for the penicillins became generally accepted, it was realized that the known routes to β-lactams probably were inadequate for a practical synthesis of penicillin (II, R = C$_6$H$_5$CH$_2$). This fact, coupled with the curious differences in the chemical properties (rate of formation, and reactivity toward certain reagents) of various β-lactams, has provoked continued research and interest in the field of the β-lactams.

Although there are at present several useful approaches to the β-lactam ring system, the synthesis of β-lactams by a single general method is not possible.   Therefore, it is always necessary in problems of β-lactam synthesis to determine which of the available methods is best suited for the case at hand.   In general, the preparation of β-lactams is more readily accomplished if the lactam being formed is highly substituted. These highly substituted β-lactams are usually more stable to ring-cleavage reactions than are the simpler β-lactams.   The method of synthesis of these stable, easily formed β-lactams is commonly determined by the availability of the starting materials.

The problem of the synthesis of the less stable, highly reactive β-lactams, e.g. a penicillin, is much more difficult.   Usually a number of the standard synthetic approaches to β-lactams are excluded at the outset because the necessary starting materials are unstable or cannot be prepared readily.   Of the remaining methods, only those that involve mild reaction conditions, and hence highly reactive starting materials, present much likelihood of success.   Thus, the outstanding problem in β-lactam synthesis is the development of new and efficient routes to the less stable β-lactams.

In principle, the synthesis of the β-lactam ring system might be accomplished by the formation of one, two, three, or all four bonds of the ring during the cyclization step.   Of these four possibilities all but the last have been realized.   All presently known routes to β-lactams in which only one bond is formed during cyclization involve formation of the amide linkage or the C_α to C_β bond.   The known syntheses of β-lactams that create two bonds all entail simultaneous formation of the same two bonds

i.e. carbonyl to nitrogen and C_α to C_β. The only reported synthesis in which three bonds are established simultaneously involves formation of all but the amide bond, and it is this route, as might be expected, that is the least general.

CYCLIZATION OF β-AMINO ACID DERIVATIVES

As mentioned earlier, the thermal dehydration of β-amino acids to β-lactams has not as yet been achieved, partly because of the ease with which β-amino acids undergo β-elimination. However, a number of β-lactams have been formed from derivatives of β-amino acids. In particular, it is noteworthy that acyl derivatives of many β-amino acids are transformed into β-lactams in good yield by heating.[3] The reaction may be illustrated by the formation of 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (V) from the N-isobutyryl derivative IV in 50–60% yield.[3]

$$\begin{array}{c} (CH_3)_2C{-}CO_2H \\ C_6H_5\overset{|}{C}H{-}NCOCH(CH_3)_2 \\ \overset{|}{C}H_2C_6H_5 \\ IV \end{array} \rightarrow \begin{array}{c} (CH_3)_2C{-}CO \\ H_5C_6\overset{|}{C}H{-}N\overset{|}{C}H_2C_6H_5 \\ V \end{array} + (CH_3)_2CHCO_2H$$
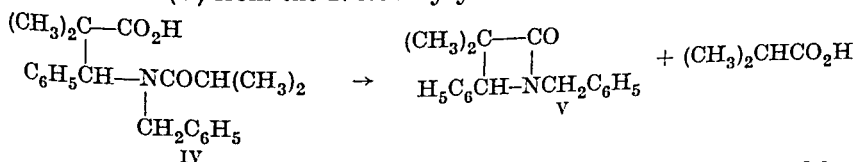
This synthesis of β-lactams from β-acylamino acids was discovered by Staudinger[3] in connection with his studies of the reaction of ketenes with imines (which also leads to β-lactams). The ketene-imine reaction often affords piperidinediones, instead of, or in addition to, β-lactams, by the combination of one molecule of imine with two of the ketene, as shown below. In these cases the β-lactam can frequently be prepared indirectly.

$$R_2C{=}NR' + 2R''C{=}C{=}O \rightarrow \begin{array}{c} R_2''C{-}C{=}O \\ O{=}C \qquad NR' \\ R_2''C{-}CR_2 \end{array} \xrightarrow{H_2O} HO_2C \begin{array}{c} R_2''CH{-}C{=}O \\ \qquad NR' \\ R_2''C{-}CR_2 \end{array}$$
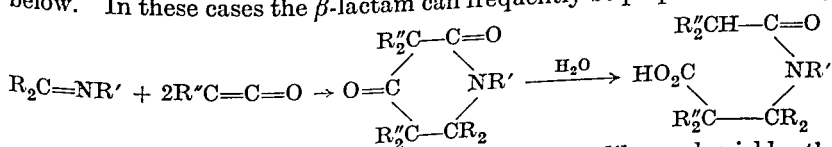
Hydrolysis of the piperidinediones proceeds readily and yields the β-acylamino acids, which can subsequently be cyclized to β-lactams. This three-step method is applicable not only to the preparation of monocyclic β-lactams but also to certain fused β-lactam-thiazolidines such as VI.[4]

$$\begin{array}{c} C_6H_5 \\ | \\ S \\ (CH_3)_2C{-}C \quad CH_2 \\ | \qquad \qquad | \\ CO{-}N{-}CH_2 \\ VI \end{array}$$
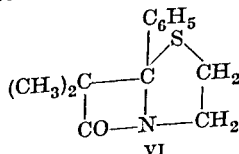
[3] Staudinger, Klever, and Kober, *Ann.*, **374**, 1 (1910).
[4] Clarke, Johnson, and Robinson, *The Chemistry of Penicillin*, Princeton University Press, 1949.

The relatively facile formation of β-lactams by this route may be due to the possibility of closing the β-lactam ring by O to N acyl rearrangement of an intermediate hydroxylactone, such as VII, in the formation of IV. Such a reaction path would explain the function of the acyl group in promoting cyclization.

$$
\begin{array}{c}
(CH_3)_2C\!\!-\!\!-\!\!-\!\!C=O \\
H_5C_6\dot{C}H \qquad O \\
N\!\!-\!\!-\!\!CCH(CH_3)_2 \\
C_6H_5\dot{C}H_2 \quad OH \\
VII
\end{array}
$$
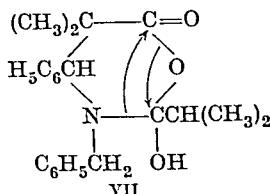
The cyclization of β-amino acids through the use of reagents such as acetyl chloride, phosphorus trichloride, and thionyl chloride has been accomplished in a limited number of cases. Thus β-benzylamino-β-phenyl-α,α-dimethylpropionic acid (VIII)[3] and β-phenyl-β-anilino-propionic acid (IX)[5] have been transformed into the corresponding β-lactams by treatment with acetyl chloride and phosphorus trichloride, respectively.

$$
\begin{array}{cc}
C_6H_5CHC(CH_3)_2CO_2H & C_6H_5CHCH_2CO_2H \\
\quad | & \quad | \\
NHCH_2C_6H_5 & NHC_6H_5 \\
VIII & IX
\end{array}
$$
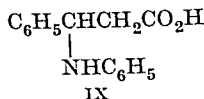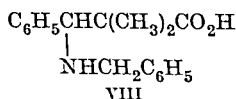
An example of a cyclization of the above type is the synthesis of a phtha-loylpenicillin (XI) from the corresponding phthaloylpenicilloic acid (X) in 12% yield by means of thionyl chloride.[6] It is interesting also to note

$$
\begin{array}{ccc}
& S & \\
XCH\!\!-\!\!-CH \quad C(CH_3)_2 & \rightarrow & XCH\!\!-\!\!-CH \quad C(CH_3)_2 \\
\quad | \qquad | \qquad | & & \quad | \qquad | \qquad | \\
HO_2C \quad HN\!\!-\!\!-CHCO_2R & & CO\!\!-\!\!N\!\!-\!\!-CHCO_2R
\end{array}
$$

X, X = phthalimido
    R = CH_3
XII, X = phenylacetamido
    R = H

XI, X = phthalimido
    R = CH_3
XIII, X = phenylacetamido
    R = H
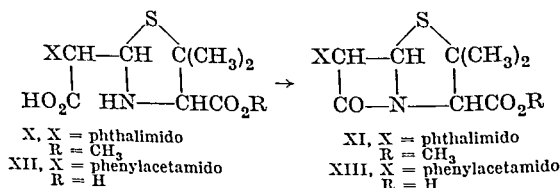
that benzylpenicilloic acid (XII) has been converted in trace yield to benzylpenicillin (XIII)[7] using phosphorus trichloride.

Another variant of the route to β-lactams via β-amino acid derivatives is due to Breckpot.[8] This synthesis, which involves the base-catalyzed cyclization of a β-amino acid ester using a Grignard reagent as the base, is illustrated by the synthesis of 1-ethyl-4-methyl-2-azetidinone (XIV).

[5] Ref. 4, p. 975.
[6] Sheehan, Henery-Logan, and Johnson, J. Am. Chem. Soc., 75, 3292 (1953).
[7] Süs, Ann., 571, 201 (1951).
[8] Breckpot, Bull soc. chim. Belg., 32, 412 (1923).

The method is especially advantageous if there are only one or two substituents on the β-lactam ring being formed, or if the substituents are alkyl groups.

$$CH_3CH-CH_2CO_2C_2H_5 \xrightarrow[40\%]{C_2H_5MgBr} \begin{array}{c} H_3CCH-CH_2 \\ | \quad\quad | \\ H_5C_2N-CO \end{array}$$

$$C_2H_5NH$$

XIV
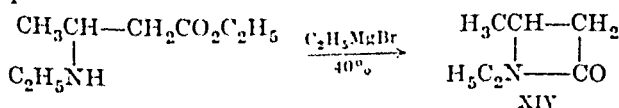
A large number of monocyclic β-lactams,[8-11] including 2-azetidinone itself,[11] have been synthesized by this method. The yields of β-lactam decrease markedly as the number of substituents on the β-lactam ring being formed decreases, but the method is frequently operable in instances where others fail. The yields obtained for a series of β-lactams possessing two, one, or no substituents are indicated below.

Compound:	H_5C_6CH-CO $CH_2-NC_6H_5$	CH_2-CO $H_3CCH-NC_2H_5$	CH_2-CO CH_2-NCH_3	CH_2-CO CH_2-NH
Yield, %:	94	40	11	0.76

Experimental Procedures

3,3-Dimethyl-1-ethyl-4-phenyl-2-azetidinone (Cyclization of a β-Acylamino Acid).[4] (a) *1-Ethyl-6-phenyl-3,3,5,5-tetramethyl-2,4-piperidinedione.* To 5.6 g. of N-benzylideneëthylamine (prepared from benzaldehyde and ethylamine) in an atmosphere of nitrogen is added a solution of 5.9 g. of dimethylketene[12] in 60 ml. of ethyl acetate. The solution becomes colorless after about six hours and is stored at room temperature for an additional fourteen hours. The ethyl acetate is removed under reduced pressure, leaving a crystalline residue weighing 8.08 g. Recrystallization from benzene-petroleum ether gives a 43% yield of colorless crystals of the piperidinedione, m.p. 89–90°.

hour (until bubbling stops). During this time 1.9 g. of isobutyric acid is collected. The pressure is reduced, and the product is distilled at 92–100°/2 mm., yielding 3.8 g. (87%) of the azetidinone.

1,4-Diphenyl-2-azetidinone (Cyclization of a β-Amino Acid).[4] A mixture of 1.2 g. of β-anilino-β-phenylpropionic acid and 2.4 ml. of phosphorus trichloride is refluxed for one-half hour. The reagent is then removed as completely as possible under reduced pressure, and the gummy residue is triturated with two 15-ml. portions of water and crystallized from cold methanol. The yield of β-lactam, m.p. 154–155°, is 0.6 g. (53%).

1-Benzyl-4-phenyl-2-azetidinone (Cyclization of a β-Amino Acid Ester).[10] To a solution of 8.01 g. of ethyl β-benzylaminohydrocinnamate[10] in 70 ml. of dry ether is added 14 ml. of a $2N$ solution of ethylmagnesium bromide in ether as rapidly as the evolution of gases permits. The mixture that results is allowed to stand at room temperature for ninety minutes and is then decomposed by cautious addition of an excess of 10% aqueous ammonium chloride. The mixture is agitated until all the solid dissolves, and the ethereal solution is separated and washed with two small portions of water. The aqueous washes are extracted with ether, and the ethereal solutions are combined, dried, and evaporated to constant weight.

The neutralization equivalent of the residual oil is determined by titration with standard hydrochloric acid. From the neutralization equivalent, the amount of standard (ca. $4N$) ethanolic hydrogen chloride required to neutralize the free amino groups is added to the oil. Most of the ethanol is removed by evaporation under reduced pressure. The residue is triturated with 25 ml. of ether, and the ethereal solution is separated from the hydrochloride by filtration. The filtrate is evaporated, and the residue is extracted with boiling ligroin. The ligroin is evaporated from the extracts, and the liquid remaining is distilled. The yield of slightly yellow 1-benzyl-4-phenyl-2-azetidinone, b.p. 145–150°/2 mm., is 3.0 g. (45%).

REACTION OF IMINES WITH α-BROMOESTERS AND ZINC

In 1943 it was discovered that the reaction of benzylideneaniline with ethyl bromoacetate and zinc produces a β-lactam, 1,4-diphenyl-2-azetidinone (XV), in 56% yield.[13] Little work has been done to determine

$$C_6H_5CH{=}NC_6H_5 + BrZnCH_2CO_2C_2H_5 \rightarrow \begin{array}{c} H_2C{-}{-}CO \\ | \quad\quad | \\ H_5C_6CH{-}NC_6H_5 \end{array}$$
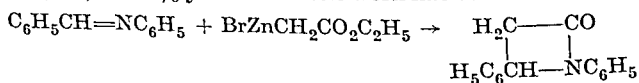
XV

[13] Gilman and Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).

the scope of this synthesis although a number of β-lactams have been prepared by this method in yields as high as 85%.[4,13] There is a strong resemblance between this reaction and that discovered by Breckpot in that both probably proceed by nucleophilic attack of an intermediate amide ion on the carbalkoxyl function with displacement of alkoxide ion and simultaneous closure of the β-lactam ring.

Experimental Procedure

1,4-Diphenyl-2-azetidinone.[13]   A solution of 36.2 g. of benzylidene-aniline in 200 ml. of dry toluene is heated to boiling with 13.5 g. of sandpapered zinc foil and a crystal of iodine.   Three milliliters of ethyl bromoacetate is added, and on stirring an exothermic reaction sets in. An additional 20 ml. of the bromoester is added at a rate such as to maintain gentle refluxing.   When the addition is complete, the mixture is heated to reflux for one-half hour.   The reaction mixture is hydrolyzed with 200 ml. of concentrated ammonium hydroxide, and the toluene layer is separated, washed successively with water, dilute hydrochloric acid, sodium bisulfite solution, and water, and finally evaporated to dryness.   Two recrystallizations of the residue from methanol afford the β-lactam, m.p. 153–154°, in 56% yield.

DIRECT COMBINATION OF KETENES WITH IMINES

The reaction of ketenes, in particular disubstituted or "ketoketenes," with imines provides a good route to some types of substituted mono- and bi-cyclic β-lactams.   Diphenylketene, for example, reacts readily with benzylideneaniline at room temperature to yield the crystalline β-lactam, 1,3,3,4-tetraphenyl-2-azetidinone (XVI) in 72% yield.[14] This was the first known β-lactam.[15]   Most of the β-lactams prepared by

$$(C_6H_5)_2C{=}C{=}O \ + \ C_6H_5CH{=}NC_6H_5 \rightarrow \begin{matrix} (C_6H_5)_2C\!\!-\!\!-\!\!CO \\ | \qquad\quad | \\ H_5C_6CH\!\!-\!\!NC_6H_5 \end{matrix}$$

XVI
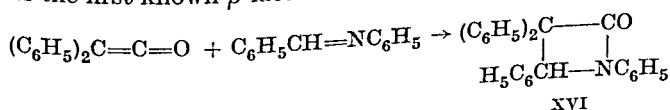
this method have been made from dimethyl-[2,16,17] or diphenyl-ketene,[2,14,18] which seem in general to react smoothly with Schiff bases derived from

[14] Staudinger, *Ann.*, **356**, 51 (1907).
[15] None of the substances that had been previously reported as β-lactams in the literature really appears to possess the β-lactam structure.   These cases are discussed in ref. 4, pp. 982–984.
[16] Staudinger and Klever, *Ber.*, **40**, 1149 (1907).
[17] Holley and Holley, *J. Am. Chem. Soc.*, **73**, 3172 (1951).
[18] Staudinger and Jelagin, *Ber.*, **44**, 365 (1911).

aromatic aldehydes or ketones and aromatic amines. Other ketenes which have been used in this synthesis include diethylketene,[19] ethylcarbethoxy-ketene,[2,20] phenylcarbomethoxyketene,[20] methylphenylketene,[2] 2,2-biphenyleneketene,[2] and ketene itself.[20] The order of reactivity for several of these ketenes toward benzophenoneanil has been determined by Staudinger to be as shown below. This order of reactivity parallels

$$\text{(naphthalene)}C{=}C{=}O > (C_6H_5)_2C{=}C{=}O > C_6H_5(CH_3)C{=}C{=}O \cong (CH_3)_2C{=}C{=}O$$
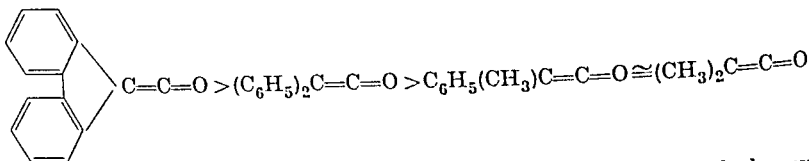
that observed by Staudinger in the reaction of ketenes with benzyl alcohol.[2] Ketene itself is much less reactive than the substituted ketenes which have been studied, for the coupling of ketene with benzylidene-aniline takes place only at temperatures near 200°.[20]

The successful use of monosubstituted ketenes, "aldoketenes," in the synthesis of β-lactams has yet to be reported. This is not surprising because monosubstituted ketenes react with imines extremely slowly and even under mild conditions show a great tendency to polymerize.[2]

The scope of the ketene-imine method for making β-lactams is limited drastically by the types and number of imines that can react to form the desired products. All but one of the β-lactams which have been prepared by this method have been obtained from imines in which both the carbon and the nitrogen atom of the imino linkage are substituted by aromatic groups. No systematic study has been made of the effect of varying the substituents on the aromatic groups, although Staudinger has found that the reactivity of benzylidene-p-nitroaniline with diphenylketene is slight compared to that of benzylideneaniline. A p-dimethylamino substituent, on the other hand, appears to increase the reactivity of aromatic Schiff bases. Perhaps it is also significant that acetophenoneanil is much less reactive to diphenylketene than is benzylideneaniline, although benzo-phenoneanil is much more reactive.[2]

Several other types of compounds containing the imino group, as for example the imido chloride XVII, the phenylhydrazone XVIII, and the oxime-ether XIX were found to be unreactive.[2,14]

$$C_6H_5C{=}NC_6H_5 \qquad C_6H_5CH{=}NNC_6H_5 \qquad C_6H_5CH{=}NOCH_3$$
$$\mid \qquad\qquad\qquad \mid$$
$$Cl \qquad\qquad\qquad CH_2C_6H_5$$
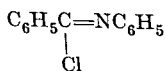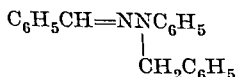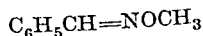
XVII   XVIII   XIX

[19] Staudinger and Maier, Ann., 401, 292 (1913).
[20] Staudinger, Ber., 50, 1035 (1917).

The presence of a sulfur substituent on the carbon of the imino grouping does not prevent β-lactam formation. The imido thioester XX reacts readily with dimethylketene to give the β-lactam XXI in 60% yield.[17]

$$(CH_3)_2C{=}C{=}O + C_6H_5C{=}NC_6H_5 \quad \rightarrow \quad \underset{\underset{\underset{SCH_3}{|}}{H_5C_6C{-}NC_6H_5}}{\overset{(CH_3)_2C{-}CO}{|\quad\quad|}}$$

$$\underset{SCH_3}{|}$$

XX   XXI
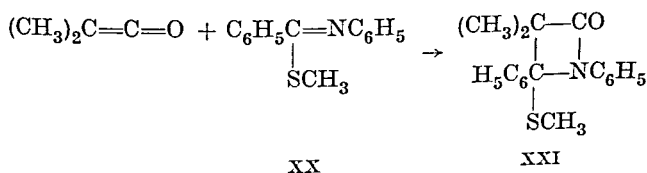
In a single instance a fused β-lactam-thiazolidine (XXII) has been prepared from 2-phenyl-2-thiazoline and diphenylketene.[21] This β-lactam served as a key model compound in the infrared studies on the structure of

$$(C_6H_5)_2C{=}C{=}O + H_5C_6\overset{S}{\underset{N{-}CH_2}{\overset{|}{C}}}CH_2 \quad \rightarrow \quad (C_6H_5)_2C{-}\overset{C_6H_5}{\underset{CO{-}N{-}CH_2}{\overset{|\ \ S}{C}}}\overset{}{\underset{}{CH_2}}$$

XXII
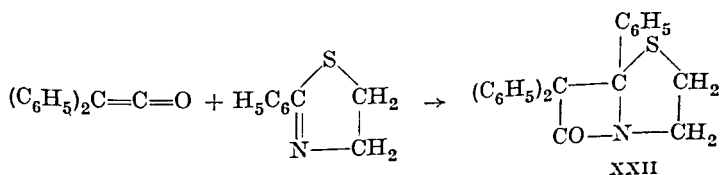
penicillin.[22] Substitution of dimethylketene for diphenylketene in the reaction with 2-phenyl-2-thiazoline does not result in formation of a β-lactam but, as mentioned previously, a piperidinedione.

Although considerable study[4] has been made of the preparation of fused β-lactam-thiazolidines closely related to penicillin by the combination of ketenes with suitable thiazolines [e.g., 2-thiazoline (XXIII) and methyl 5,5-dimethyl-2-thiazoline-4-carboxylate (XXIV)], no successful results have been reported.

XXIII   XXIV
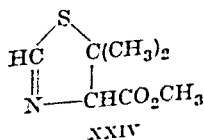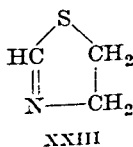
There are two cases in which the reaction of ketenes with imines is of special interest. The first is the combination of diphenylketene with cinnamylideneaniline which has been shown to lead to the β-lactam XXV instead of the δ-lactam XXVI to be expected from 1,4 addition.[14,23]

[21] Ref. 4, p. 996.
[22] Ref. 4, p. 405.
[23] Penicillin Program Report, Shell 14, 215.

The occurrence of 1,2 instead of 1,4-addition strikingly demonstrates the increased ease of formation of highly substituted β-lactams.

$$(C_6H_5)_2C\text{---}CO$$
$$C_6H_5CH\text{=}CHCH\text{---}NC_6H_5$$

XXV

$$(C_6H_5)_2C\text{---}CO$$
$$H_5C_6CH \qquad NC_6H_5$$
$$CH\text{=}CH$$
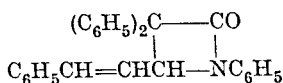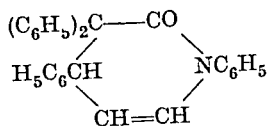
XXVI

The reaction of ethylcarbethoxyketene (XXVII) with benzylidene-aniline occurs readily at $-10°$ to give a crystalline 1 : 1 adduct which is not the β-lactam XXVIII and which was formulated by Staudinger as XXIX. The adduct is unstable and decomposes slowly at room temperature into the original imine and ketene. Upon heating this compound

$$C_2H_5C\text{=}C\text{=}O$$
$$CO_2C_2H_5$$

XXVII

$$C_2H_5$$
$$C_2H_5O_2CC\text{---}CO$$
$$H_5C_6CH\text{---}NC_6H_5$$

XXVIII

$$C_2H_5$$
$$C_2H_5O_2CC\text{---}CO$$
$$H_5C_6N\text{---}CHC_6H_5$$
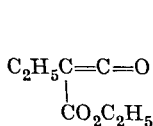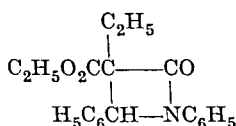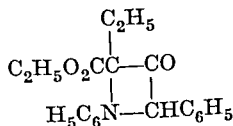
XXIX

at 170° the isomeric β-lactam XXVIII is formed. The β-lactam can also be obtained directly from the ketene and the imine at 180°. At present there is no cogent evidence in favor of structure XXIX for the unstable adduct, and structure XXX must be regarded as being at least equally possible.

$$C_2H_5OC\text{=}CC_2H_5$$
$$O \qquad CO$$
$$H_5C_6CH\text{---}NC_6H_5$$
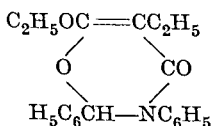
XXX

Phenylcarbomethoxyketene (XXXI) which might be expected to be more reactive to 1,2-addition than ethylcarbethoxyketene yields a β-lactam directly with benzylideneaniline. No intermediate product has been isolated. Dicarbethoxyketene (XXXII), on the other hand, does not appear to afford a β-lactam with benzylideneaniline under any conditions.

$$C_6H_5$$
$$CH_3O_2C\diagup C\text{=}C\text{=}O$$

XXXI

$$(C_2H_5O_2C)_2C\text{=}C\text{=}O$$

XXXII

$$C_6H_5CH_2CONHCOCH_2N_2$$
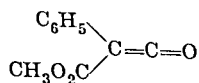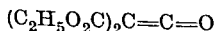
XXXIII

Several unsuccessful attempts have been made to form β-lactams by the combination of imines with the rearrangement products, presumably

ketenes, of diazo ketones. The reaction of phenylacetylcarbamyldiazo-methane (XXXIII) with methyl 5,5-dimethyl-2-thiazoline-4-carboxylate in the presence of silver oxide, which might have afforded methyl benzyl-penicillinate, produced a complex mixture which had little or no bioactivity.[24]

Experimental Procedure

2,α,α-Triphenyl-2-thiazolidineacetic Acid β-Lactam.[4] Three and nine-tenths grams of diphenylketene[25] is added to 3.3 g. of 2-phenyl-2-thiazoline.[26] After five minutes the spontaneous heating ceases, and the mixture is warmed to 60–70° for five minutes. The product is taken up in warm toluene, diluted with low-boiling petroleum ether and cooled to give 4.5 g. of the β-lactam (63% yield) as a colorless solid, m.p. 140–143°.

REACTION OF KETENES WITH NITROSO COMPOUNDS

During the course of an investigation of the reaction of ketenes with nitroso compounds, Staudinger and Jelagin[18] found that equimolar amounts of diphenylketene and nitrosobenzene gave a 63–65% yield of a product assigned structure XXXIV, and that a 2:1 molar ratio of the ketene and nitroso compound gave a mixture of products consisting mainly of XXXIV together with a small amount of the β-lactam XXXV.[18] It was suggested that the β-lactam is formed by addition of diphenylketene to benzophenoneanil which is produced by the decarboxylation of the

$$\begin{array}{ccc} (C_6H_5)_2C{-}CO & (C_6H_5)_2C{-}CO & (C_6H_5)_2C{-}CO \\ |\quad\ | & |\quad\ | & | \\ O{-}NC_6H_5 & (C_6H_5)_2C{-}NC_6H_5 & H_5C_6N{-}O \\ \text{XXXIV} & \text{XXXV} & \text{XXXVI} \end{array}$$
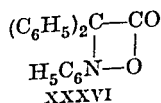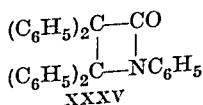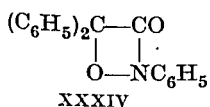
intermediate XXXVI. p-Dimethylaminonitrosobenzene, which was found to be more reactive than nitrosobenzene, afforded a 65% yield of the β-lactam when treated with two moles of diphenylketene and yielded no product corresponding to XXXIV. Nitroso derivatives of secondary amines such as diphenylamine and diethylamine do not react with diphenylketene to give β-lactams.[18]

REACTION OF AN IMINE, AN ACID CHLORIDE, AND A TERTIARY AMINE

One of the most recent syntheses of β-lactams, developed in connection with the problem of penicillin synthesis, involves the combination of an imine or thiazoline and an acid chloride, with loss of hydrogen chloride,

[24] Ref. 4, p. 990.
[25] *Org. Syntheses*, **20**, 47 (1940).
[26] Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).

in the presence of a tertiary amine.[27,28] An example of this synthesis is the reaction of benzylideneaniline with phthaloylglycyl chloride in the presence of triethylamine to give 1,4-diphenyl-3-phthalimido-2-azetidinone (XXXVII) in 50% yield.[27] The reaction proceeds rapidly at room temperature in inert solvents. By hydrazinolysis of the phthaloyl group

$$XCH_2COCl + C_6H_5CH{=}NC_6H_5 \xrightarrow{C_6H_6} \begin{array}{c} H_5C_6CH{-}NC_6H_5 \\ | \qquad\qquad | \\ XCH{-}CO \end{array} + (C_2H_5)_3\overset{+}{N}H\overset{-}{Cl}$$
$$+\ (C_2H_5)_3N$$
$$\text{XXXVII}$$
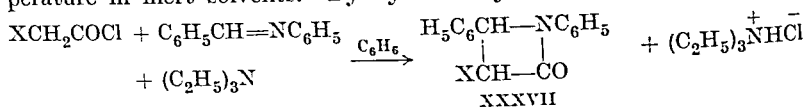
X = Phthalimido

the phthalimido β-lactam XXXVII can be converted to an amino β-lactam and thence to other acylamino derivatives.[27]

Thiazolines bearing a 2-aryl or 2-carbalkoxy substituent also yield β-lactams in this reaction. Thus, 2-phenyl-,[28] 2-p-nitrophenyl-,[29] and 2-furyl-thiazolines[30] react with phthaloylglycyl chloride and triethylamine to give good yields of the corresponding β-lactams.
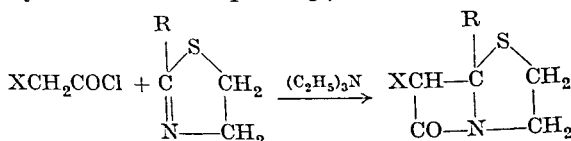
The synthesis of a 5-phenylpenicillin (XXXIX) has been carried out by this approach, using methyl 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylate (XXXVIII) and succinylglycyl chloride as indicated below.[31,32]

X = succinimido

1. OH⁻; H⁺
2. CH₂N₂

XXXIX
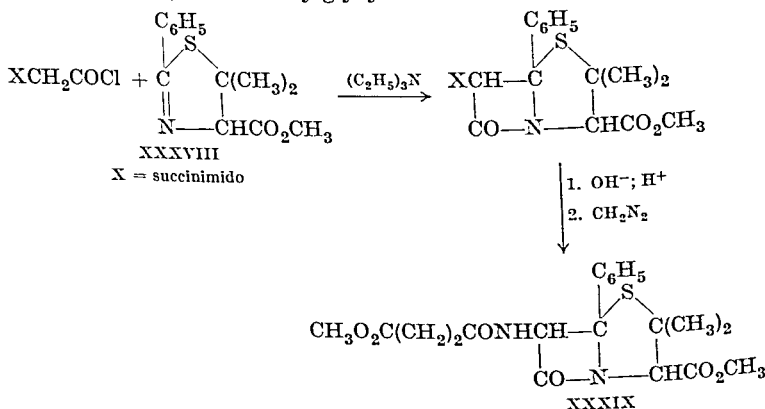
[27] Sheehan and Ryan, J. Am. Chem. Soc., **73**, 1204 (1951).

[28] Sheehan and Ryan, J. Am. Chem. Soc., **73**, 4367 (1951).

[29] J. C. Sheehan and K. Henery-Logan, unpublished results.

[30] E. J. Corey, Ph.D. Thesis, Massachusetts Institute of Technology, 1951; J. A. Erickson, Ph.D. Thesis, Massachusetts Institute of Technology, 1953.

[31] Sheehan, Buhle, Corey, Laubach, and Ryan, J. Am. Chem. Soc., **72**, 3828 (1950).

[32] Sheehan and Laubach, J. Am. Chem. Soc., **73**, 4376 (1951).

The acid chloride-thiazoline reaction is apparently very sensitive to the nature of the ring substituents. No lactam was isolated with thiazolines possessing a hydrogen, sulfhydryl, or chlorine substituent in the 2-position.[33] In addition, the reaction proceeds better with 2-phenyl-2-thiazoline than with methyl 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylate, while ethyl 2-phenyl-2-thiazoline-4-carboxylate is intermediate in behavior. Thus, the yields of β-lactam obtained with these three thiazolines are 50%,[28] 20%,[34] and 34%[35] respectively.

To date the acid chloride-imine synthesis has been applied only to the synthesis of acylamino β-lactams. The acid chlorides that have been used successfully in the reaction include phthaloyl- and succinyl-glycyl chloride, 5-phenyl-2,4-diketo-3-oxazolidineacetyl chloride[36] (XL), and 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride[37] (XLI). The last two substances were employed because the heterocyclic systems which they contain can be degraded, once the β-lactam ring has been formed, to the phenylacetylamido substituent which is characteristic of benzyl-penicillin (II, $R = C_6H_5CH_2$). These degradations are indicated by the accompanying formulas.[36,37]
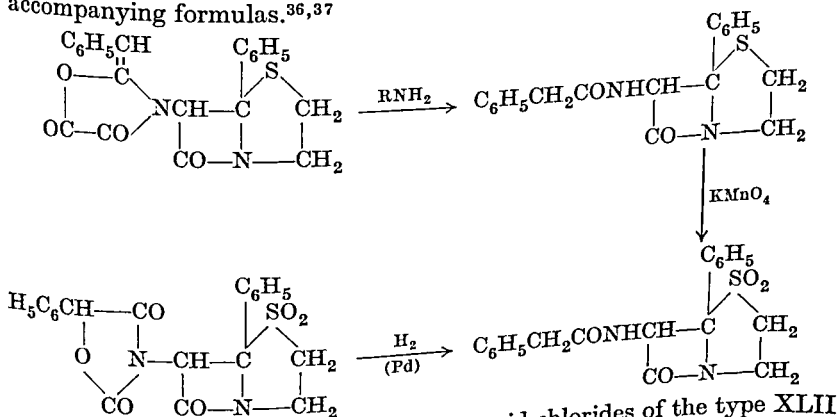
It is important to note that acylamino acid chlorides of the type XLII are not generally available for use in the acid chloride-thiazoline synthesis

$$RCH_2CONHCH_2COCl \qquad RCH_2CONHCH_2CO_2H \rightarrow$$

XLII

XLIII
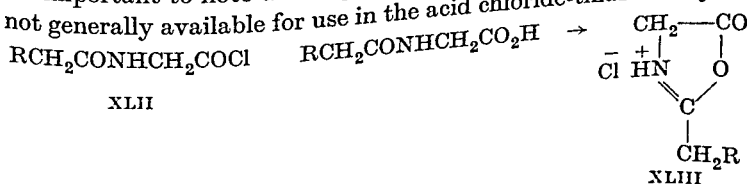
[33] J. C. Sheehan and co-workers, unpublished observations.
[34] Sheehan, Hill, Jr., and Buhle, J. Am. Chem. Soc., 73, 4373 (1951).
[35] D. A. Johnson, Ph.D. Thesis, Massachusetts Institute of Technology, 1952.
[36] Sheehan and Laubach, J. Am. Chem. Soc., 73, 4752 (1951).
[37] Sheehan and Corey, J. Am. Chem. Soc., 73, 4756 (1951).

since attempts to obtain them from the corresponding acids usually lead to
formation of salts of azlactones (XLIII). Thus, it is necessary to employ
systems in which the nitrogen atom is protected from azlactonization by
the presence of a suitable blocking group.

Benzenesulfonylglycyl chloride (XLIV) and carbobenzoxyglycyl
chloride (XLV), which cannot azlactonize but which possess an unpro-
tected nitrogen atom, react with benzylideneaniline to form 4-imidazolones
in yields of about 75%.[38]

$$RNHCH_2COCl + \begin{matrix} CHC_6H_5 \\ \| \\ NC_6H_5 \end{matrix} \xrightarrow{(C_2H_5)_3N} \begin{matrix} R \\ | \\ N \\ \diagup \diagdown \\ CH_2 \quad CHC_6H_5 \\ | \qquad | \\ CO—NC_6H_5 \end{matrix}$$

$$XLIV \quad R = C_6H_5SO_2$$
$$XLV \quad R = C_6H_5CH_2OCO$$
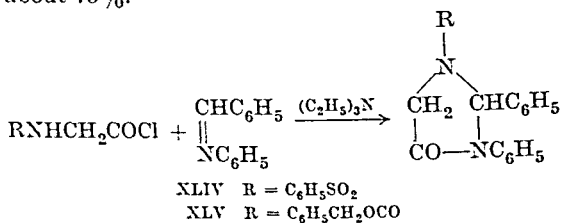
Although it is clear at present that the acid chloride-imine (or thiazoline)
reaction is by no means general for acid chlorides or imines, the exact scope
of the reaction is still unknown. In addition, nothing is known about
the mechanism of the reaction. Under some conditions there have been
isolated crystalline by-products which have been tentatively formulated
as acyl derivatives of enolized piperidinediones on the basis of elemental
and infrared analysis.[28,31] The formation of such by-products can
usually be minimized by working at very high dilution and operating
with refluxing chloroform rather than methylene chloride as the
solvent.[28,30,31]

2-Phenyl-α-succinimido-2-thiazolidineacetic Acid β-Lactam.[32]

To a solution of 1.63 g. of 2-phenyl-2-thiazoline[26] in 10 ml. of methylene chloride (dried over Drierite) in a 200-ml. three-necked flask is added 1.85 g. of succinylglycyl chloride in 25 ml. of methylene chloride. To this rapidly stirred solution at reflux is added through a high-dilution cycle[39] a solution of 1.02 g. of triethylamine in 50 ml. of methylene chloride over a six-hour period. The resulting amber solution is concentrated under reduced pressure to a brown magma, which is shaken with 50 ml. of benzene. The colorless, crystalline residue of triethylammonium chloride (1.50 g., ca. 100%) is removed by filtration, and the filtrate is concentrated to a brown oil which partially crystallizes on standing for several days. The mixture is triturated with 20 ml. of 50% aqueous ethanol, allowed to stand overnight, and filtered. The crude lactam, crisp yellow needles, m.p. 148–160°, weighing 1.70 g., is purified by recrystallization from dioxane-water (Norit). The yield of essentially pure lactam, m.p. 166–168°, is 0.9 g. (30%).

DEHYDROHALOGENATION OF N-α-HALOACYLAMINOMALONIC ESTERS

Another reaction sequence by which a β-lactam can be formed is the establishment of an amide linkage by chloroacetylation of a substituted aminomalonic ester and subsequent base-catalyzed ring closure by the formation of a carbon-carbon bond. A specific example is furnished by the preparation of 1-phenyl-4,4-dicarbethoxy-2-azetidinone (XLVI) from anilinomalonic ester.[40]

$$C_6H_5NHCH(CO_2C_2H_5)_2 + (ClCH_2CO)_2O \rightarrow \underset{\overset{|}{COCH_2Cl}}{C_6H_5NCH(CO_2C_2H_5)_2} \quad (92\%)$$

$$\Big\downarrow (C_2H_5)_3N$$

$$\underset{\underset{XLVI}{CO-CH_2}}{\overset{H_5C_6N-C(CO_2C_2H_5)_2}{\overset{|}{}\overset{|}{}}} \quad (95\%)$$

$$\underset{\underset{XLVII}{CO-CH_2}}{\overset{H_5C_6N-CHCO_2C_2H_5}{\overset{|}{}\overset{|}{}}} \quad \overset{Two\ steps}{\longleftarrow}$$

The reaction appears to be general for N-substituted aminomalonic esters N-acylated with α-haloacids, and the yields obtained are invariably high.[40,41] No dimeric or linear condensation products have been observed. The exact nature of the basic reagent is not important since triethylamine, diethylamine, benzylamine, alcoholic ammonia, and alcoholic potassium

[39] Cope and Herrick, J. Am. Chem. Soc., 72, 983 (1950).
[40] Sheehan and Bose, J. Am. Chem. Soc., 72, 5158 (1950).
[41] Sheehan and Bose, J. Am. Chem. Soc., 73, 1761 (1951).

hydroxide all have been used successfully in the ring-closure.[41] The β-lactams obtained by this process can be converted to β-lactams bearing a single carbethoxy substituent, e.g. XLVII, by selective hydrolysis of one ester function and decarboxylation of the resulting acid.

This method of synthesis, although efficient, is obviously restricted to the preparation of β-lactams which possess one or two carboxyl (or similar) functions at the 4-position. A further limitation results from the fact that N-unsubstituted N-haloacylaminomalonic esters containing a hydrogen atom attached to the nitrogen atom, such as XLVIII, apparently do not undergo cyclization upon treatment with tertiary amines or other bases.[41]

$$ClCH_2CONHCH(CO_2C_2H_5)_2$$
XLVIII

Experimental Procedure

1-Phenyl-3-ethyl-4,4-dicarbethoxy-2-azetidinone.[41] A solution of 2 g. of α-bromo-n-butyric acid, 1 ml. of phosphorus trichloride, and 2 g. of diethyl anilinomalonate[42] in 50 ml. of benzene is heated under reflux for two hours. After removal of the solvent, the residue is taken up in ether and washed with 5% aqueous sodium carbonate. Evaporation of the ether affords 2.84 g. of crude diethyl N-(α-bromo-n-butyryl)-anilinomalonate as a viscous oil. A benzene solution of this crude material containing 2 g. of triethylamine is heated to 50–60° overnight. After removal of the insoluble triethylammonium chloride and solvent and evaporative distillation of the residue at 130–145°/0.4 mm., 2.29 g. (78% yield based on the malonic ester) of β-lactam is obtained as a colorless, viscous liquid, n_D^{25} 1.5108.

MISCELLANEOUS SYNTHESES

An unusual approach to the β-lactam ring system is provided by the reaction of diazomethane with isocyanates. Diazomethane and phenyl isocyanate combine, in a manner reminiscent of the formation of cyclobutanone from ketene and diazomethane, to form 1-phenyl-2-azetidinone.[43] p-Bromophenylisocyanate is also converted to a β-lactam under these conditions. The reaction does not appear to be general, however, since no β-lactam could be isolated from the reaction of diazomethane with either α-naphthyl-, p-nitrophenyl-, benzyl-, or benzoyl-isocyanate.

Several β-lactams have been prepared by modification of the substituents present in preformed β-lactam systems. Examples were mentioned in

[42] Blank, *Ber.*, **31**, 1812 (1898).
[43] Sheehan and Izzo, *J. Am. Chem. Soc.*, **70**, 1985 (1948); **71**, 4059 (1949).

the preceding sections. Perhaps the best-known example of such a conversion, however, is the synthesis of methyl desthiobenzylpenicillinate (XLIX) by desulfurization of methyl benzylpenicillinate with Raney nickel.[4]

$$C_6H_5CH_2CONHCH\underset{\overset{|}{CO}—\overset{}{N}—\overset{|}{CH}CO_2CH_3}{\overset{S}{—\overset{|}{CH}\quad \overset{|}{C}(CH_3)_2}} \xrightarrow[H_2]{Ni}$$

$$C_6H_5CH_2CONHCH\underset{\overset{|}{CO}—\overset{}{N}—\overset{|}{CH}CO_2CH_3}{\overset{}{—\overset{|}{CH_2}\quad \overset{|}{CH}(CH_3)_2}}$$

XLIX
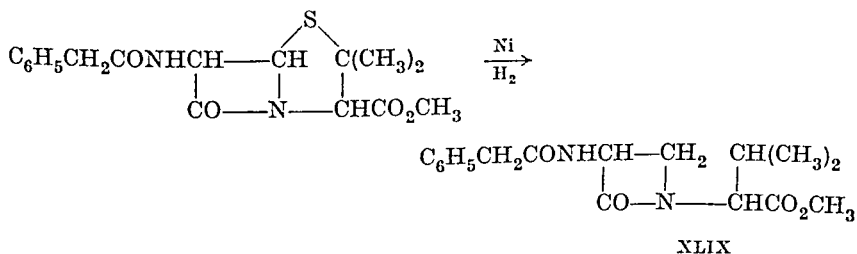
Oxidation of fused β-lactam-thiazolidines produces, in general, the corresponding β-lactam-thiazolidine-1,1-dioxides in good yield.[4]

Finally, a number of β-lactams substituted by cyclohexyl groups have been prepared by catalytic reduction of the corresponding phenyl-substituted β-lactams.[4]

TABULAR SURVEY OF SYNTHESES OF β-LACTAMS

An attempt has been made to collect in the following tables all examples of β-lactam syntheses that have been published before 1953. A few syntheses published subsequently are also included. Table I includes monocyclic β-lactams, and Table II the fused β-lactam thiazolidines. The sections of each table are arranged in a sequence determined by the number of substituents on the β-lactam ring. The following abbreviations are used for preparative methods: A, cyclization of β-amino acid esters with organometallic compounds; B, cyclization of β-acylamino acids; C, from β-amino acids; D, from imines, α-bromoesters, and zinc; E, from ketenes and imines; F, from ketenes and nitroso compounds; G, from acid chlorides, imines, and tertiary amines; H, dehydrohalogenation of N-α-haloacylaminomalonic esters; I, from isocyanates and diazomethane; J, from a preformed β-lactam.

TABLE I—*Continued*

Monocyclic β-Lactams—Azetidinones

$$\alpha C\!\!-\!\!\!-\!\!\!-\!\!C\!\!=\!\!O$$
$$\begin{array}{cc}|3 & 2| \\ |4 & 1| \end{array}$$
$$\beta C\!\!-\!\!\!-\!\!\!-\!\!N$$
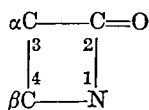
β-Lactam (Substituents on Azetidinone Ring)	Yield, %	Method of Preparation	Reference
Trisubstituted—Continued			
1,4-Diphenyl-3-amino (hydrochloride)	54	J	27
1,4-Diphenyl-3-phenylacetamido	56	J	27
1,4-Diphenyl-3-(2′-benzylidene-4′,5′-diketo-3′-oxazolidyl)	17	J	37
	16	G	37
1,4-Diphenyl-3-(3′-nitrophthalimido)	54	G	27
1,4-Diphenyl-3-dimethanesulfonamido	39	G	38
1,4-Diphenyl-3-methanesulfonamido	—	J	38
Tetrasubstituted			
1,3,3-Trimethyl-4-phenyl	65	B	3, 4
1-Benzyl-3,3-dimethyl-4-phenyl	10	E	3
	70	C	4
	50–60	B	3
1,4-Diphenyl-3,3-dimethyl	—	E	16
1,4-Diphenyl-3,3-diethyl	82	E	19
1,4-Diphenyl-3-ethyl-3-carbethoxy	1	E	20
1,3,4-Triphenyl-3-carbomethoxy	—	E	20
1,3,3,4-Tetraphenyl	72	E	16
1,3,3-Triphenyl-4-styryl	70	E	14
1-Phenyl-3,3-dimethyl-4-p-dimethylaminophenyl	—	E	2
1-Benzhydryl-3,3-dimethyl-4-phenyl	—	E	2
1-Phenyl-3,3-dimethyl-4-styryl	—	E	2
1-p-Nitrophenyl-3,3-dimethyl-4-phenyl	—	E	2
1-Ethyl-3,3-dimethyl-4-phenyl	87	B	4
1,3,4-Triphenyl-3-methyl	—	B	44
1-Phenyl-3-methyl-4,4-dicarbobenzoxy	ca. 90	H	41
1-Phenyl-3-ethyl-4,4-dicarbethoxy	ca. 90	H	41
Pentasubstituted			
Pentaphenyl	84	E	18
	—	F	18
1-p-Dimethylaminophenyl-3,3,4,4-tetraphenyl	100	E	18
	65	F	18
1,4,4-Triphenyl-3,3-dimethyl	—	E	2
1,4-Diphenyl-3,3,4-trimethyl	—	E	2
1,3,4,4-Tetraphenyl-3-methyl	—	E	2
1,4,4-Triphenyl-3,3-o-biphenylene	—	E	2
1,4-Diphenyl-3,3-dimethyl-4-methylmercapto	60	E	17

[41] Staudinger and Ruzicka, *Ann.*, 380, 301 (1911).

CHAPTER 7

THE PSCHORR SYNTHESIS AND RELATED DIAZONIUM RING CLOSURE REACTIONS

DeLos F. DeTar
University of South Carolina

CONTENTS

INTRODUCTION

In the middle eighteen nineties three groups of chemists independently discovered a new cyclization reaction of certain appropriately constituted diazonium salts. Fischer and Schmidt[1] reported that an aqueous
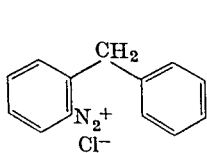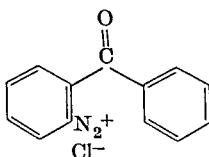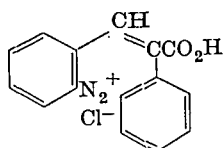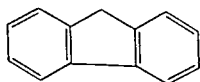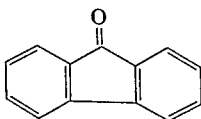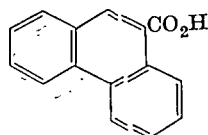
solution of 2-benzylbenzenediazonium chloride (I) furnished fluorene (II) on heating. Graebe and Ullmann[2] reported that 2-benzoylbenzene-

---

[1] Fischer and Schmidt, *Ber.*, **27**, 2786 (1894).
[2] Graebe and Ullman, *Ber.*, **27**, 3483 (1894).

diazonium chloride (III) yielded fluorenone (IV), and Staedel[3] reported a somewhat similar result from the action of nitrous acid on 2,2'-diamino-benzophenone, a reaction that produced a little 1-hydroxyfluorenone. Two years later Robert Pschorr[4] applied the ring closure reaction to the diazonium salt derived from *trans*-2-amino-α-phenylcinnamic acid (V) (aryl groups *cis*) to obtain phenanthrene-9-carboxylic acid (VI). The principal utility of these cyclization reactions has been the synthesis of substituted ring structures in which the positions of the substituents are known. In a series of papers Pschorr[5–21] reported the application of the reaction to the synthesis of a large number of phenanthrene derivatives with special emphasis on morphine degradation products. Although Pschorr was not the first to use the reaction, he was the first to exploit it extensively for the determination of structure. The phenanthrene synthesis, appropriately known as the Pschorr reaction, is still the best known of the various diazonium cyclization reactions. Various aspects of the cyclization reactions of diazonium salts have been reviewed previously.[22–25]

MECHANISMS OF THE REACTIONS

Comparison with the Gomberg-Bachmann Synthesis

Intermolecular analogs of the cyclization reactions have been recognized for many years. Pschorr[4] pointed out their similarity to the biphenyl

[3] Staedel, *Ber.*, 27, 3362 (1894).

[4] Pschorr, *Ber.*, 29, 496 (1896).

[5] Pschorr, Wolfes, and Buckow, *Ber.*, 33, 162 (1900).

[6] Pschorr, *Ber.*, 33, 176 (1900).

[7] Pschorr and Sumuleanu, *Ber.*, 33, 1810 (1900).

[8] Pschorr and Jaeckel, *Ber.*, 33, 1826 (1900).

[9] Pschorr and Buckow, *Ber.*, 33, 1829 (1900).

[10] Pschorr, Seydel, and Klein, *Ber.*, 34, 3998 (1901).

[11] Pschorr and Schröter, *Ber*, 35, 2726 (1902).

[12] Pschorr, Seydel, and Stöhrer, *Ber.*, 35, 4400 (1902).

[13] Pschorr and Vogtherr, *Ber.*, 35, 4412 (1902).

[14] Pschorr, Stählin, and Silberbach, *Ber.*, 37, 1926 (1904).

[15] Pschorr, Tappen, Hofmann, Quade, Schütz, and Popovici, *Ber.*, 39, 3106 (1906).

[16] Pschorr and Busch, *Ber.*, 40, 2001 (1907).

[17] Pschorr and Zeidler, *Ann.*, 373, 75 (1910).

[18] Pschorr and Knöffler, *Ann.*, 382, 50 (1911).

[19] Pschorr, Selle, Koch, Stoof, and Treidel, *Ann.*, 391, 23 (1912).

[20] Pschorr, Zeidler, Dickhäuser, Treidel, and Koch, *Ann.*, 391, 40 (1912).

[21] Avenarius and Pschorr, *Ber.*, 62, 321 (1929).

[22] Saunders, *The Aromatic Diazo-compounds and Their Technical Applications*, 2d ed., p. 254, Longmans, Green & Co., New York, 1949.

[23a] Holzach, *Die Aromatischen Diazoverbindungen*, p. 231, Ferdinand Enke, Stuttgart, 1947.

[23b] Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., pp. 8, 29, Reinhold Publishing Co., New York, 1949.

[24] Leake, *Chem. Revs.*, 56, 27 (1956).

[25] Hey and Osbond, *J. Chem. Soc.*, 1949, 3164.

syntheses of Möhlau and Berger[26] which employed a diazonium salt, an aromatic solvent, and anhydrous aluminum chloride, and to those of
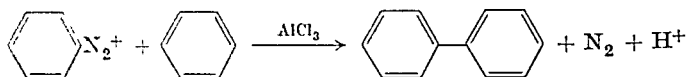
Kühling and of Bamberger[27] which were forerunners of the Gomberg-Bachmann reaction. More recently the analogy has generally been drawn with the Gomberg-Bachmann reaction itself[28,29] a typical example of which is the preparation of *m*-nitrobiphenyl by the reaction of *m*-nitrobenzenediazonium chloride, benzene, and alkali in a two-phase system.
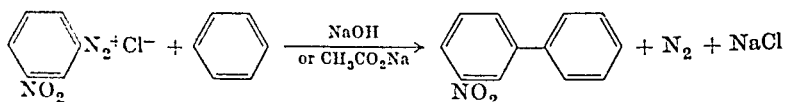
There are, however, a number of points of difference between the two-phase, alkaline, Gomberg-Bachmann reactions and the cyclization reactions. Many of the cyclization reactions, e.g. the fluorenone syntheses, are carried out in acidic solutions. Such systems are initially single phase and only incidentally become multiphase owing to precipitation of reaction products. The Pschorr reaction is usually carried out in strongly acidic solution in the presence of copper powder. In a few cases it has been carried out in a homogeneous alkaline solution. Thus, in considering the mechanisms of the cyclization reactions, evidence concerning these intermolecular reactions is helpful but must be interpreted with due caution.

Evidence for a Heterolytic Cyclization

Preliminary work on the mechanisms of the cyclization reactions[30-31] has shown that the fluorenone synthesis as usually carried out takes place by a heterolytic[35] (ionic) mechanism as shown in the equation. On the other hand, the copper-catalyzed Pschorr reactions may occur by a homolytic (free-radical) chain mechanism, though adequate evidence is

VII
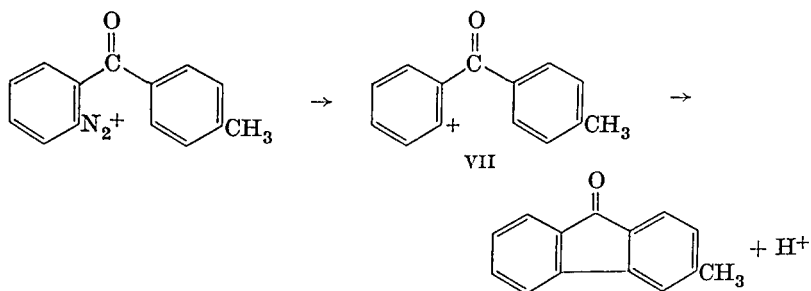
not yet available. The diazonium cyclization reactions therefore appear to belong to a lengthening list of reactions that occur by more than one mechanism.

Evidence for a heterolytic fluorenone formation is derived from (1) general studies of the mechanisms of diazonium salt reactions and (2) specific studies of the fluorenone cyclization reaction.

There is good evidence based both on rate studies and on product studies with several diazonium salts that in water and in alcohols the thermal decomposition of the diazonium group is a heterolytic process under acidic conditions in the absence of light or of reducing agents, and that under alkaline conditions the decomposition takes place at least in part by homolytic processes.

The evidence for a heterolytic mechanism for the thermal decomposition of several diazonium salts in acidic aqueous solutions is based on the observation that the reaction is accurately first order over the full course $(10–99\%)$[36-38] and is independent of the presence of or absence of a large variety of anions, or of acidity, over a considerable pH range. This independence rules out various homolytic mechanisms involving hypothetical intermediate covalent diazo compounds such as the diazo chloride, $C_6H_5N=NCl$, or diazo hydroxide, $C_6H_5N=NOH$. The diazonium cation itself can give rise to radicals only by reactions yielding ionized nitrogen or water molecules and hence requiring prohibitively high energies. Thus homolytic mechanisms are excluded by the kinetic evidence.

$$C_6H_5N_2^+ \rightarrow C_6H_5\cdot + (\cdot N:::N:)^+$$
$$C_6H_5N_2^+ + H_2O \rightarrow C_6H_5\cdot + (H:\ddot{O}:H)^+ + N_2$$
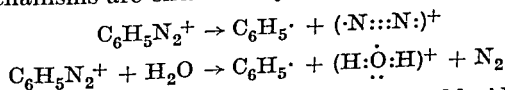
Product studies show that benzenediazonium chloride reacts with methanol under acidic conditions to give high yields (90–95%) of anisole.[39] In the presence of sodium acetate the principal product is benzene (85–90%), and the reaction is very sensitive to oxygen. Such results

[36] DeTar and Ballentine, *J. Am. Chem. Soc.*, **78**, 3916 (1956).
[37] DeTar and Kwong, *J. Am. Chem. Soc.*, **78**, 3921 (1956).
[38] Moelwyn-Hughes and Johnson, *Trans. Faraday Soc.*, **36**, 948 (1940).
[39] DeTar and Turetzky, *J. Am. Chem. Soc.*, **77**, 1745 (1955); **78**, 3925, 3928 (1956).

require a homolytic mechanism in the presence of the acetate buffer and a heterolytic mechanism under acidic conditions.

In water the reaction of diazonium salts in the presence of alkali is highly complex, and the problem of unraveling mechanisms is difficult. However, the two-phase Gomberg-Bachmann reaction clearly requires some sort of homolytic mechanism as shown by the excellent orientation studies of Hey and his co-workers.[40] The activating effect and the ortho-para directing effect of the nitro group of nitrobenzene afford perhaps the clearest single item of evidence in favor of a homolytic mechanism for the Gomberg-Bachmann reaction.

The fluorenone ring closure occurs readily under acidic conditions. Accordingly, a heterolytic mechanism seems most probable. This hypothesis is easily subject to further experimental investigation by use of appropriately substituted benzophenones in the ring closure reaction. The thermal decomposition of the diazonium salts derived from 2-aminobenzophenone in aqueous solution gave 65% of fluorenone and 35% of 2-hydroxybenzophenone, these two products together accounting quantitatively for the starting material.[31] The product ratio and yield were insensitive to temperature in the range 25–75°. These products are ascribed to two competing heterolytic displacement reactions of the diazonium nitrogen; the one, intermolecular, involving a water molecule as the nucleophilic reagent and the other, intramolecular, involving an aryl group as the nucleophilic reagent.

Since a methyl group enhances and a nitro group diminishes the nucleophilic capabilities of the aryl ring, a methyl group should increase and a nitro group decrease the yield of fluorenone if the reaction is heterolytic. But, since the nitro group is an activating group for homolytic substitution reactions,[40] the ring closure should be more favored
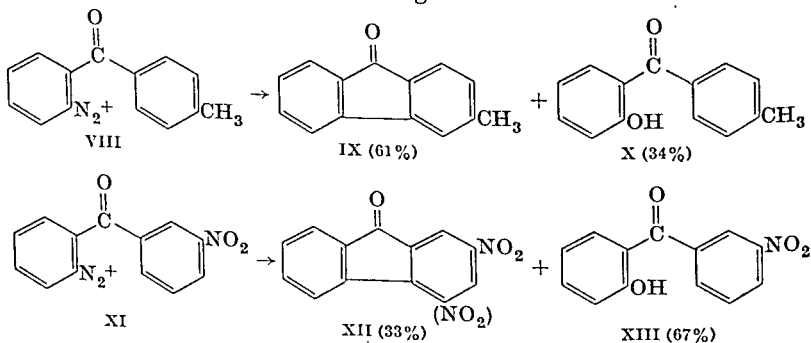
[40] Augood, Cadogan, Hey and Williams, *J. Chem. Soc.*, **1953**, 3412, and earlier papers. See also DeTar and Scheifele, *J. Am. Chem. Soc.*, **73**, 1442 (1953); Dannley and Gippin, *ibid.*, **74**, 332 (1952); Rondestvedt and Blanchard, *ibid.*, **77**, 1769 (1955).

with the nitro derivative if the reaction is homolytic. The yields given in the equations show that the methyl group of VIII is without effect, though the nitro group of XI does diminish the fluorenone yield. The results are, therefore, in satisfactory agreement with predictions based on a heterolytic mechanism for the ring closure. The small effect of the substituents on the product ratio and yield, kinetic evidence, and certain other product evidence have been cited[31] as favoring an S_N1 loss of nitrogen rather than an aromatic S_N2 type of replacement.

Products of the Homolytic Reaction

Under alkaline conditions the diazonium salts derived from 2-amino-benzophenone can be expected to react to some extent by a mechanism involving homolytic C—N bond cleavage. With alkali present (pH 12), only about 25% of fluorenone is produced. A similar reduction in yield under alkaline conditions has been observed for many of the diazonium cyclization reactions. In view of the demonstrated simultaneous occurrence of heterolytic and homolytic mechanisms,[39] it is not at all certain that even these low yields of fluorenone have resulted from free-radical intermediates.

The usual hypothesis about the mechanistic details of the homolytic Gomberg-Bachmann reaction is shown in the equation. The substituting radical is pictured as adding to the aromatic ring to give the new radical
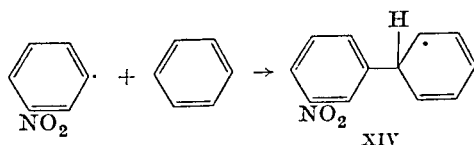
XIV which loses a hydrogen atom to some other radical present in the solution. The intramolecular version of this step ($XV \rightarrow XVI$) might
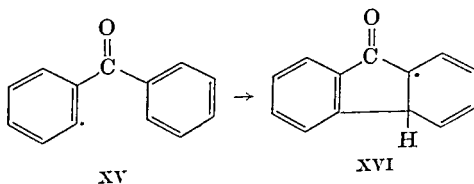
be expected to occur even more readily by virtue of the proximity of the radical to the potential reaction site. Reactions in which there is closure of a five-membered ring usually occur much more readily than their intermolecular counterparts. For some unknown reason the o-benzoyl-phenyl radical (XV) does not undergo this cyclization reaction at all readily in comparison with competing reactions. Treatment of diazotized

2-amino-4'-methylbenzophenone (VIII) with alkali and with carbon tetrachloride leads to 3-methylfluorenone (IX), 2-chloro-4'-methylbenzophenone (XVII), and 2-chloro-4-methylbenzophenone (XVIII).[33,34]   The 2-(4'-methylbenzoyl)phenyl radical (XIX) evidently reacts with carbon
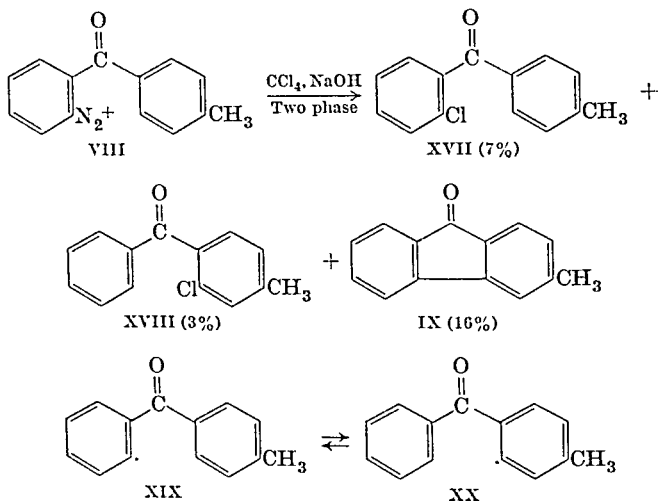
tetrachloride to abstract a chlorine atom to give 2-chloro-4'-methylbenzophenone (XVII) and with itself by an intramolecular chain transfer step to give the isomeric radical XX, which leads to 2-chloro-4-methylbenzophenone (XVIII).   Even if all of the 3-methylfluorenone is ascribed to free-radical cyclization of XIX or XX, the free-radical cyclization is a relatively inefficient process.   The chlorobenzophenones XVII and XVIII are not expected from a carbonium ion intermediate.   Although the general possibility of chlorine abstraction from carbon tetrachloride by a carbonium ion intermediate has perhaps not yet received a really rigorous investigation, the formation of the chlorobenzophenone XVIII from the carbonium ion VII is unlikely in view of the ease with which this ion cyclizes.   Further evidence pointing to inefficiency of the free-radical cyclization step is the fact that the Gomberg-Bachmann reaction of diazotized 2-aminobenzophenone with benzene in the presence of alkali gives a 20% yield of 2-phenylbenzophenone (XXI) and little fluorenone. If these reactions are formulated as radical substitution processes, it is strange
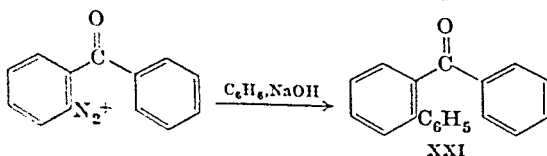
that an intermolecular reaction should take precedence over an intramolecular one, especially since the carbonyl group is expected to aid the cyclization process, for the carbonyl group is probably an activating group for free-radical substitution reactions.[40]

Preliminary studies of the Pschorr reaction with the diazonium salt derived from cis-2-aminostilbene (XXII) have provided results quite different from the above.[32] The thermal decomposition in aqueous solutions gives low yields of nitrogen and of phenanthrene (15–40%), the yields being higher at 100° than at 25°. A search was made for a nitrogen-containing by-product which was thought likely to be 3-phenyl-cinnoline. The product turned out to be indazole (XXIII). Several workers had previously reported benzaldehyde in reactions of this type, but no one had isolated the other cleavage fragment.[41–43] These results then seem to typify the heterolytic process in the phenanthrene series.

XXII   XXIII
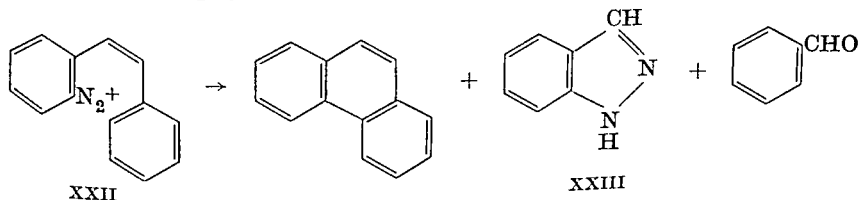
If copper powder is present, the reaction is faster and the phenanthrene yield is higher (60–85%). It may be that the copper is promoting a homolytic reaction as has been suggested by Waters,[28] or perhaps some quite different intermediate steps are involved. The assumption of a homolytic process finds some support in work on the mechanism of the reduction of diazonium salts with hypophosphorous acid, a free-radical chain reaction that is initiated by copper.[44] Treatment of diazotized cis-2-aminostilbene with hypophosphorous acid leads to phenanthrene, not to cis-stilbene.[42] Furthermore, sodium hypophosphite and copper powder have been used in a number of Pschorr reactions. Examples are to be found in Table I.

SCOPE AND LIMITATIONS
Examples of Different Types of Bridge

The diazonium cyclization reaction has been carried out with compounds having a number of different types of bridge. To the examples already mentioned (I, III, and V) may be added compounds XXIV–XXXIII.

[41] Sachs and Hilpert, Ber., 39, 899 (1906); Ullmann and Gschwind, Ber., 41, 2291 (1908).
[42] Ruggli and Staub, Helv. Chim. Acta, 19, 1288 (1936); 20, 37 (1937).
[43] Simpson, J. Chem. Soc., 1943, 447.
[44] Kornblum, Cooper, and Taylor, J. Am. Chem. Soc., 72, 3013 (1950).

(The percentages following the Roman numerals indicate the yield of normal Pschorr cyclization products.)
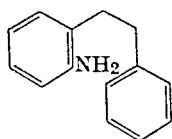
XXIV >20%[42]
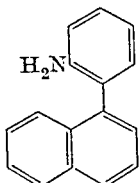
XXV 48%[45]
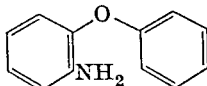
XXVI 45%[30]
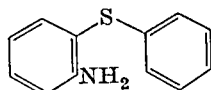
XXVII 40%[46]
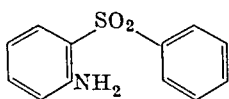
XXVIII <30%[30]
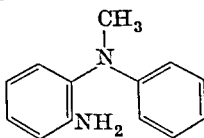
XXIX 67%[47]
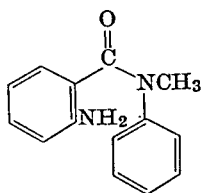
XXX 50%[48]
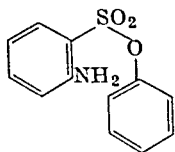
XXXI 52%[49]
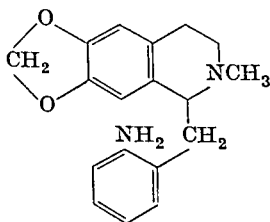
XXXII 24%[50,51]
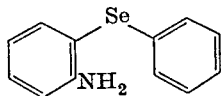
XXXIII trace[46]

For the success of the cyclization reaction the carbon atoms that are to be linked together must be near each other. Perhaps the most favorable bridging group is the rigid ethylenic bridge of a *cis*-2-aminostilbene derivative (V and XXII). The corresponding *trans* ethylenic derivative undergoes other reactions typical of the diazonium group,[32,42] but is quite

Aq. H_2SO_4
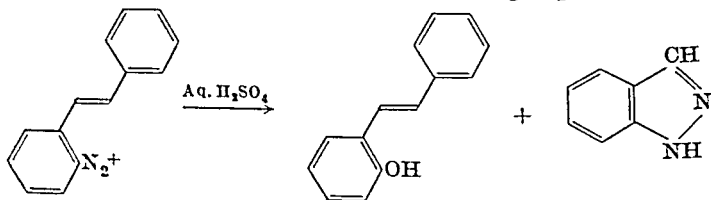
[42] Forrest and Tucker, *J. Chem. Soc.*, 1948, 1137.
[45] Cullinane, Rees, and Plummer, *J. Chem. Soc.*, 1939, 151.
[47] Hey and Mulley, *J. Chem. Soc.*, 1952, 2276.
[48] Heacock and Hey, *J. Chem. Soc.*, 1952, 1508.
[49] Schetty, *Helv. Chim. Acta*, 32, 24 (1949).
[50] Barger and Weitnauer, *Helv. Chim. Acta*, 22, 1036 (1939).
[51] Marion and Grassie, *J. Am. Chem. Soc.*, 66, 1290 (1944).

incapable of giving phenanthrene. Hey and Mulley have calculated the distance of closest approach between the two relevant carbon atoms for several compounds (1.5 Å for V and XXII, 2.0 Å for XXIX, 2.2 Å for I, and 2.4 Å for III).[47] The calculated values are rather sensitive to the angle of the C—X—C bond of the bridge; unfortunately this angle is not accurately known for most of the systems of interest, and hence present calculations cannot be expected to have quantitative significance. However, the estimates do clearly show that the stilbene derivatives have the most favorable spacing. There is a definite decline in yield of cyclic product with increasing bridge size as in the sulfide XXVII and the sulfone XXVIII, while the still larger selenide XXXIII gave only traces of cyclic product. Electrical factors seem to play a somewhat secondary role. The decrease in yield from 65% for fluorenone (IV) or for 3-methylfluorenone (IX) to 35% for the nitrofluorenones (XII)[31] is important practically, but relatively small as such effects go. (Compare the factor of about a million in the difference in the rates of nitration of benzene and of nitrobenzene.) For the most part the data available are insufficient to permit an appraisal of the importance of the electrical effect of the groups present. Generally such effects may be neglected in planning a synthesis.

However, there is one electrical effect that seems to be of some importance. When a hydroxyl group is *ortho* to a diazonium group, a diazo oxide is formed (XXXIV). An *ortho*-quinoid structure is a possible resonance form even if the oxygen atom is part of an ether (XXXV). Similar structures are possible with *ortho* amino groups. Such structures may be responsible for resin-forming side reactions that often occur with compounds such as XXVI and XXXVI containing an oxygen atom or a nitrogen atom *ortho* to the diazonium function.[52]
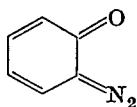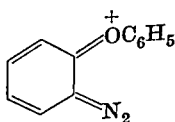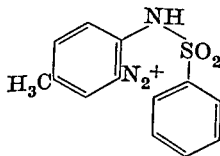
XXXIV   XXXV   XXXVI

Side Reactions

Because the diazonium group is highly reactive, a number of reactions with external reagents can compete successfully at the expense of the cyclization. Examples of four such reactions follow.

[52] Ullmann and Gross, *Ber.*, **43**, 2694 (1910).

Replacement of the Diazonium Group by Hydroxyl. This reaction is always a potential competitor. Examples are the formation of 2-hydroxy-4'-methylbenzophenone (X) and 2-hydroxy-3'-nitrobenzophenone (XIII), both of which were mentioned earlier (p. 414).

Replacement of the Diazonium Group by Hydrogen. This occurs in the presence of reagents known to promote such a replacement. For example, sodium hypophosphite and copper convert diazotized *cis*-2-aminostilbene (XXII) into phenanthrene in an 80% yield.[42] However, this combination is of little use outside the phenanthrene series since diazonium salts less susceptible to ring closure give the normal replacement by hydrogen.[44] Diazotized *sym*-2-aminodiphenyl-ethane (XXIV) is thus converted into *sym*-diphenylethane rather than into 9,10-dihydrophenanthrene.[42] The use of alcohols as solvents also can lead to reduction.[53] A copper suspension in aqueous or in organic media sometimes gives reduction products even though such obvious hydrogen sources as the alcohols are absent.[54,55]
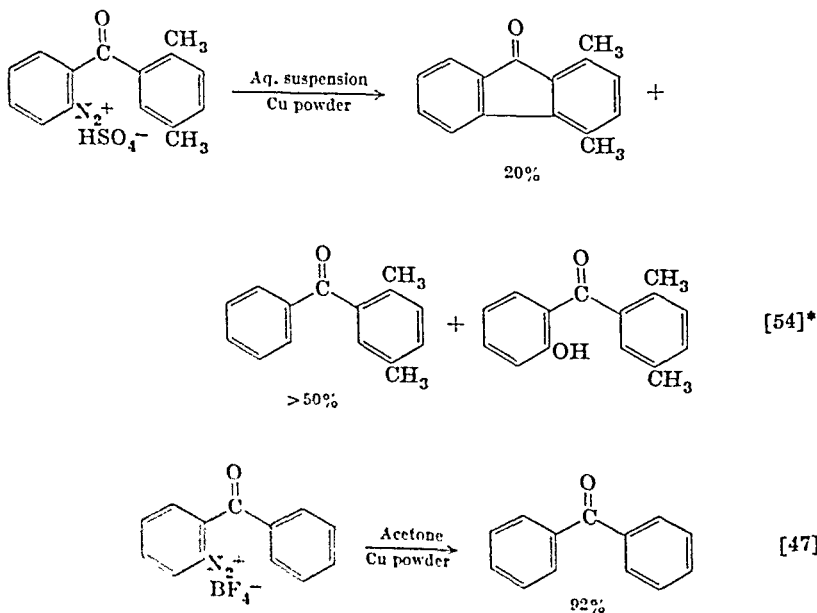
Replacement of the Diazonium Group by Halogen. The Gattermann reaction usually does not occur, but can compete if excess hydrochloric acid is present. A recently suggested procedure involving formation and decomposition of a triazene sometimes gives chlorine-containing by-products.[25]

$$\text{Dry HCl} \atop \text{Benzene}$$

60% 10% [25]
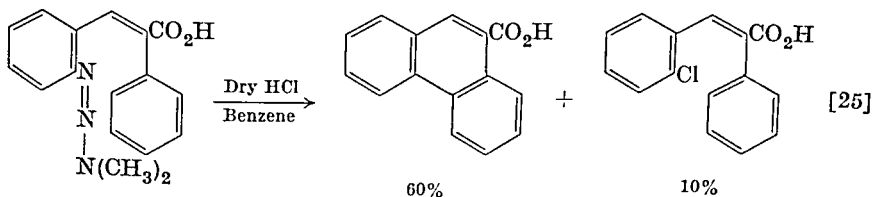
Coupling of the Aryl Groups. The Vorländer-Meyer[56] coupling of diazonium salts leads either to biphenyl derivatives or to azobenzene derivatives. Ammoniacal cuprous hydroxide is one of the best reducing agents for the coupling reaction when this reaction is desired. The coupling side reaction has not usually been reported, but may well be the cause of some of the low yields obtained.

$$\frac{\text{Cu}}{\text{Acetone}}$$

24% 35% [47]

$+ o\text{-HOC}_6\text{H}_4\text{CH}_2\text{C}_6\text{H}_5$

22%

$+ \text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_5$

$$\frac{\text{H}_2\text{O}}{\text{Cu}}$$

50% 25% [47]
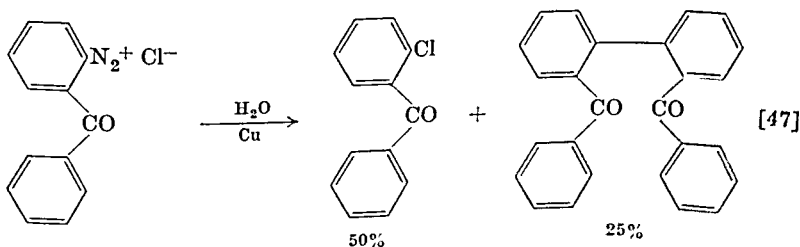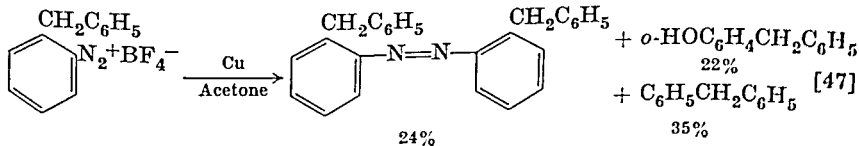
In addition to side reactions due to external agents, there are a number of side reactions that can occur intramolecularly.

Formation of Xanthones. An alkoxyl group in the 2'-position interferes with many of the cyclization reactions. In the fluorenone series the product is a xanthone derivative, e.g. XXXVII,[57-59] rather

than a fluorenone derivative. The failure of diazotized *trans*-2-amino-α-(2'-furyl)cinnamic acid (XXXVIII) to give identifiable products may have
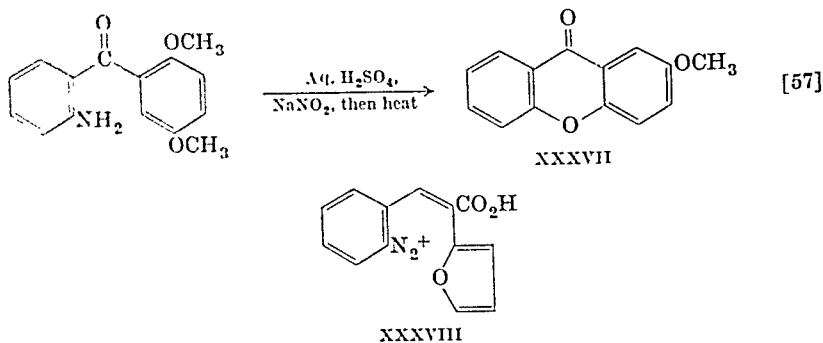
been a result of the occurrence of reaction at the oxygen atom rather than at the 3-position of the furan ring.[60]

Elimination of Carboxyl and Nitro Groups. Examples of the elimination of 2'-nitro groups and of 2'-carboxyl groups have been reported. The 2'-nitro group of diazotized 2-amino-2'-nitrobenzophenone (XXXIX) is eliminated to an appreciable extent.[47] The 2'-nitro group of 2-amino-2'-nitro-N-methyldiphenylamine (XL) is largely eliminated if copper
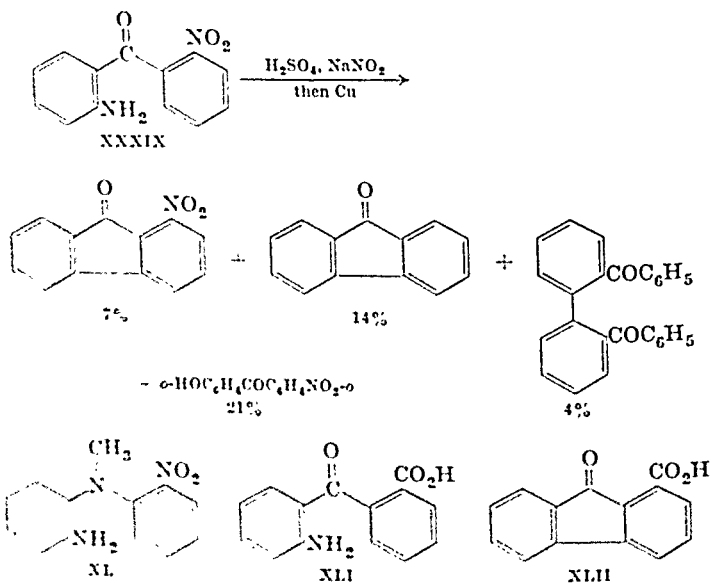
powder is used in the decomposition of the diazonium salt, and largely retained if the copper is omitted.[47]   Thermal decomposition in aqueous sulfuric acid solution of the diazonium salt derived from 2-amino-2'-carboxybenzophenone (XLI) in the absence of copper led to approximately 10% yields each of fluorenone and of fluorenone-1-carboxylic acid (XLII).[61]   Side reactions of these types seem to be less important in the phenanthrene series, though detailed product studies have yet to be made. Thus several 1-methoxy- and 1-carboxy-phenanthrene derivatives (XLIII–XLV) have been prepared by the Pschorr reaction.[5,15,62]
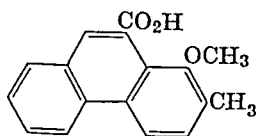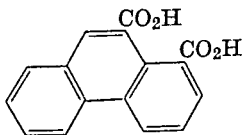
XLIII   XLIV
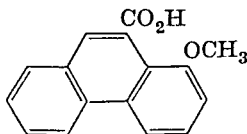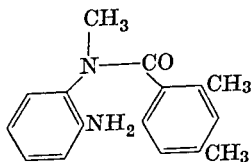
XLV   XLVI

Deamination in Phenanthridone Syntheses.   An intramolecular hydrogen abstraction and resultant demethylation reaction has been reported[63,64] in an attempted preparation of 4-substituted phenanthridones from 2-substituted N-(2'-aminobenzoyl)-N-methylanilines.[65]   Incidentally the phenanthridone ring closure has usually been unsuccessful if

[63, 65]
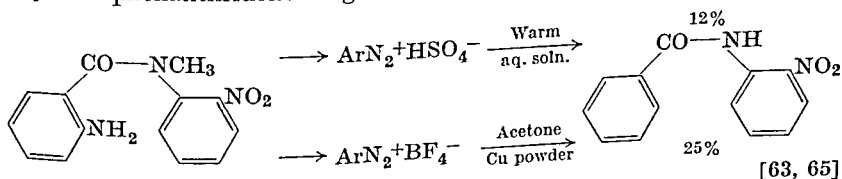
the amino group is not in the benzoyl ring; the amide XLVI gave no phenanthridone.[66]

[61] Sieglitz, *Ber.*, **57**, 316 (1924).
[62] Hill and Short, *J. Chem. Soc.*, **1937**, 260.
[63] Hey and Turpin, *Chemistry & Industry*, **216**, 216, 221 (1954).
[64] Forrest, Haworth, Pinder, and Stevens, *J. Chem. Soc.*, **1949**, 1311.
[65] Heacock and Hey, *J. Chem. Soc.*, **1953**, 3.
[66] Chardonnens and Würmli, *Helv. Chim. Acta*, **33**, 1338 (1950).

Simpson[43] has discussed in admirable fashion the factors that lead to cinnoline formation rather than to carbon cyclization. The diazonium salt derived from cis-2-(1'-naphthyl)-1-(2"-aminophenyl)-1-phenylethene
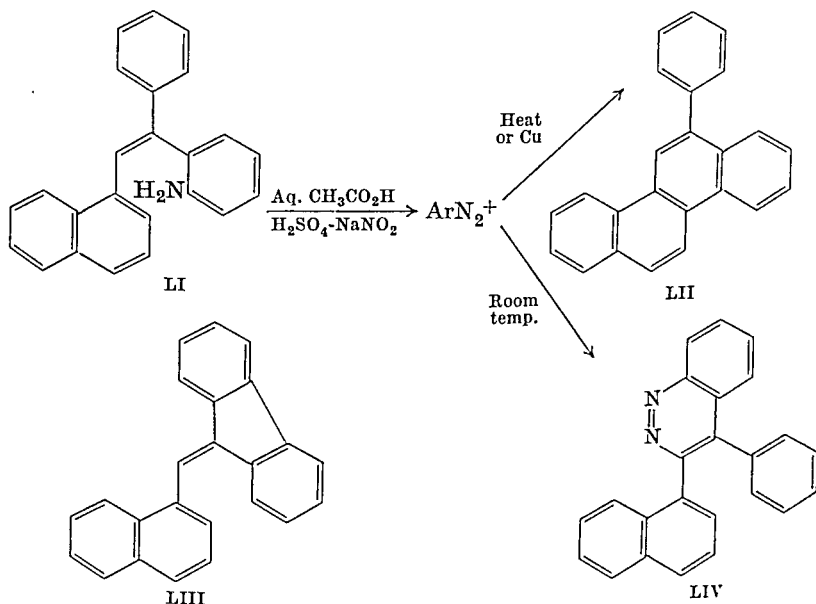
(LI) reacted on warming to give 2-phenylchrysene (LII). The presence or absence of 9-(1'-naphthylmethylene)fluorene (LIII) was not ascertained. At room temperature 3-(1'-naphthyl)-4-phenylcinnoline (LIV) was the major product. Cinnoline formation, like the indazole (XXIII) production observed with diazotized cis-2-aminostilbene (XXII), evidently has a lower activation energy than does loss of nitrogen, for nitrogen elimination is favored by high reaction temperatures. In general, the presence on the ethylenic bridge of electron-releasing groups aids and the presence of electron-attracting groups hinders cinnoline formation. With a carboxyl group present on the bridge, cinnoline formation does not occur.

Cinnoline ring closure occurs if an active methylenic bridge is present; the ketone LV gives the cinnoline LVI rather than the phenanthrol LVII.
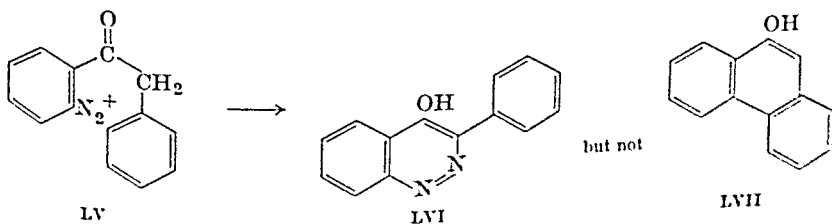
If a secondary amino group is in a position to form a five- or six-membered ring by coupling with the diazonium group, the coupling will usually take place in preference to loss of nitrogen. Examples are the formation of the triazine derivative LVIII from diazotized 2-amino-

LVIII

LIX   LX

LXI
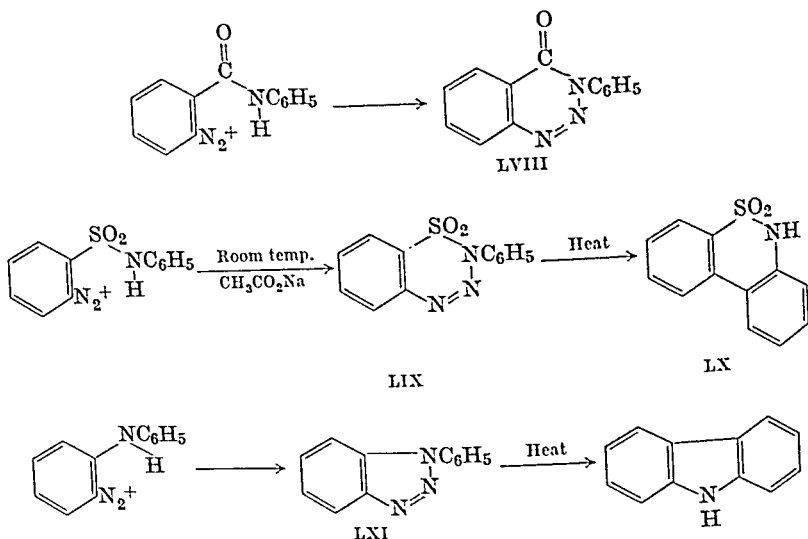
benzanilide,[68] the formation of the thiatriazine derivative LIX from diazotized 2-aminobenzenesulfonanilide,[52] and the formation of 1-phenylbenzotriazole (LXI) from diazotized 2-aminodiphenylamine.[69] Carbon cyclization has been achieved in two of the examples. If the diazotized 2-aminobenzenesulfonanilide is heated, the sultam (LX) of 2'-aminobiphenyl-2-sulfonic acid is obtained. Furthermore, many 1-arylbenzotriazoles such as LXI are converted to carbazole derivatives with loss of nitrogen when they are heated to 250–400°.

Factors Affecting the Direction of Ring Closure

In the cyclization reaction there are sometimes two or more possible products of the ring closure. Such possibilities always arise when substituents in the 3'- and 5'-positions of the aryl ring to which closure is made are not identical, providing that both the 2'- and the 6'-positions are free. Examples are given in the equations. Such reactions are usually to be avoided.

[68] König and Reissert, *Ber.*, **32**, 782 (1899). See, also, Pictet and Gonset, *Arch. sci. phys. nat. Genève.* [4] **3**, 37 (1897) (*Chem. Zentr.*, **1897**, I, 413).

[69] Graebe and Ullmann, *Ann.*, **291**, 16 (1896).

[70]

[71]

[31]
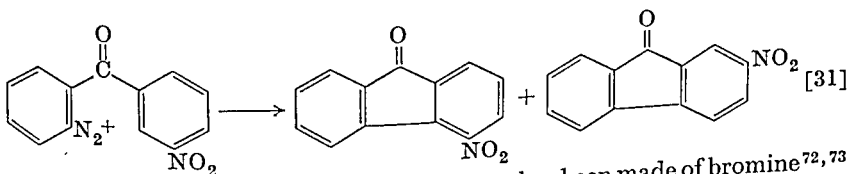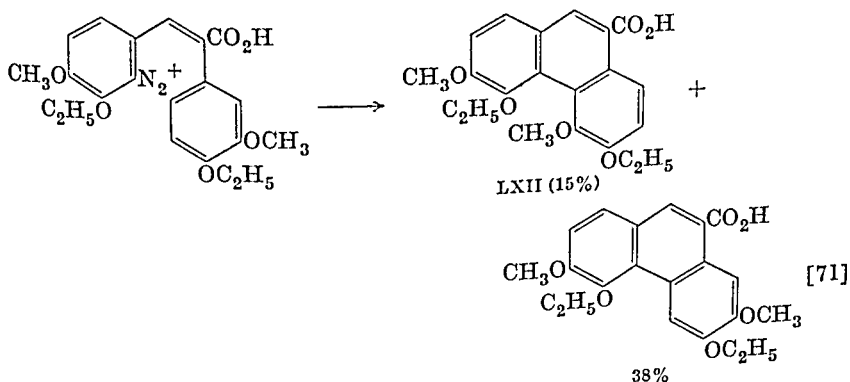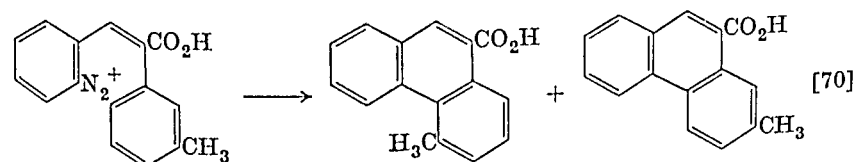
In the phenanthrene series considerable use has been made of bromine[72,73] in the 6'-position as a blocking group, the bromine being removed eventually by reduction. Although the phenanthrene ring can be formed with

[72]
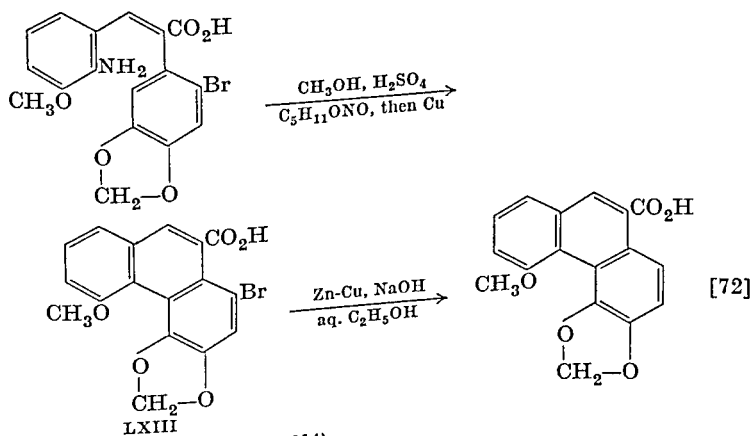
[70] Mayer and Balle, *Ann.*, **403**, 167 (1914).
[71] Späth and Tharrer, *Ber.*, **66**, 904 (1933).
[72] Girardet, *Helv. Chim. Acta*, **14**, 513 (1931).
[73] Lewis and Elderfield, *J. Org. Chem.*, **5**, 290 (1940).

two alkoxyl groups in the 4- and 5-positions as shown by LXII and LXIII, two alkyl groups in the 4- and 5-positions are too bulky to permit closure. No identifiable product was obtained from the reaction of diazotized

LXIV

LXV

LXVI

LXVII
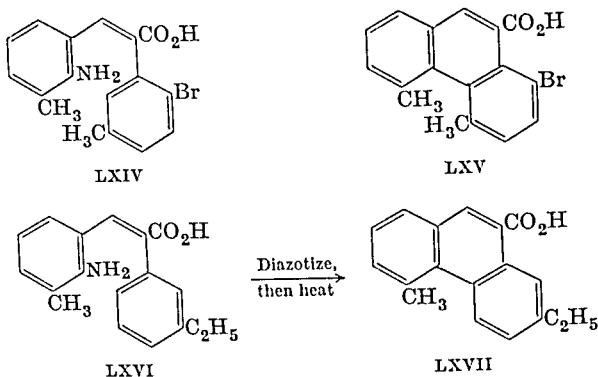
trans-2-amino-3-methyl-α-(2'-bromo-5'-methylphenyl)cinnamic acid (LXIV).[73] (The acid LXV was *not* formed.) It is possible to use this effect to advantage in preparing dialkylphenanthrene derivatives. Diazotized *trans*-2-amino-3-methyl-α-(3'-ethylphenyl)cinnamic acid (LXVI) gave a good yield of 7-ethyl-4-methylphenanthrene-9-carboxylic acid (LXVII), uncontaminated with the 4,5-isomer.

With a 1-naphthyl group in the α-position of the cinnamic acid, closure takes place in the 2-position rather than in the 8-position. *trans*-2-Amino-α-(1'-naphthyl)cinnamic acid (LXVIII) when diazotized and treated with copper powder and sodium hypophosphite gave chrysene-5-carboxylic

LXVIII

LXIX (28%)

[74]

LXX

LXXI

[75]
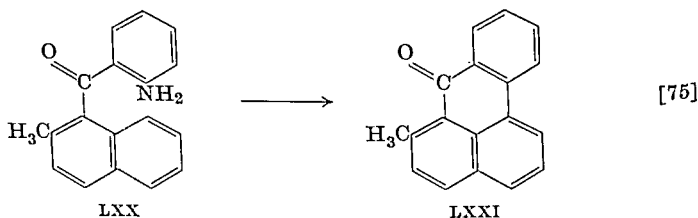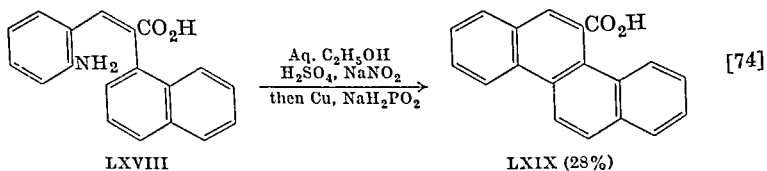
[74] Fieser and Joshel, *J. Am. Chem. Soc.*, **62**, 1211 (1940).
[75] Lothrop and Goodwin, *J. Am. Chem. Soc.*, **65**, 363 (1943).

acid (LXIX). The 1-naphthyl ketone LXX in which the 2-position is blocked does, however, give a small yield of the 1,8-cyclization product LXXI.

With a 2-naphthyl group, closure takes place to the 1-position in preference to the 3-position. This is illustrated by the reaction of diazotized *trans*-2-amino-α-(2'-naphthyl)cinnamic acid (LXXII) to give primarily benzo[c]phenanthrene-6-carboxylic acid (LXXIII).[76]

LXXII   LXXIII (6%)   LXXIV (0.6%)
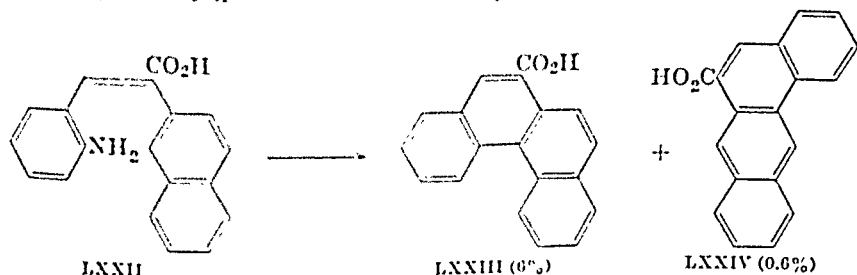
Simultaneous Closure of Two Rings

A few examples of the simultaneous closure of two rings have been reported. The *m*-phenylenediacetic acid derivative LXXV gave dibenz-[aj]anthracene-6,8-dicarboxylic acid (LXXVI) and 2,2'-diamino-6,6'-diphenylbiphenyl (LXXVII) gave dibenzo[el]pyrene (LXXVIII).

LXXV   LXXVI   [77]

LXXVII   LXXVIII   [78]
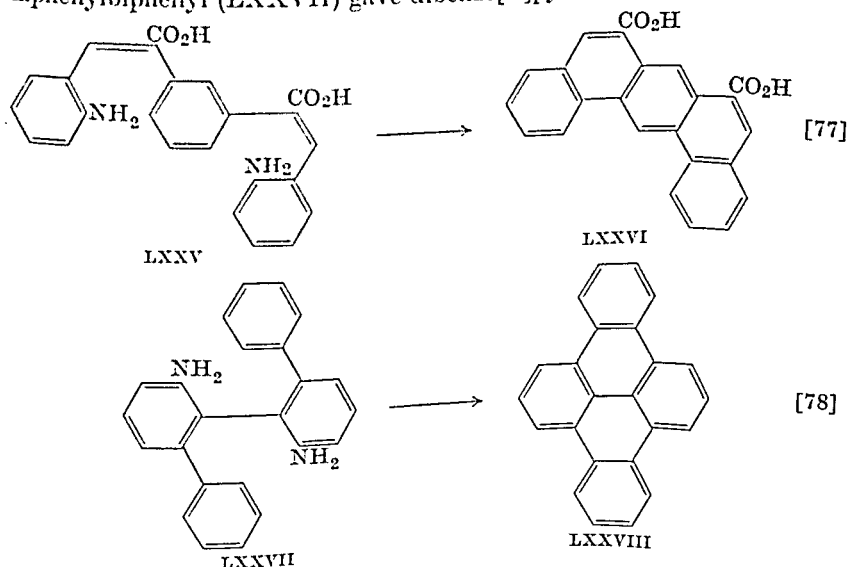
[76] Cook, *J. Chem. Soc.*, **1931**, 2524.
[77] Cook, *J. Chem. Soc.*, **1932**, 1472.
[78] Sako, *Bull. Chem. Soc. Japan*, **9**, 55 (1934) [*C. A.*, **28**, 3730 (1934)].

Aliphatic Analogs

Simple aliphatic amines appear not to undergo ring closure. Geissman and Tess[79] report that the treatment of 2-aminomethylbiphenyl (LXXIX) with sodium nitrite in aqueous acetic acid yields 2-biphenylmethanol. The details reported do not seem to exclude entirely the possibility of some fluorene production. The action of nitrous acid on 3-phenylpropylamine

$$\xrightarrow[\text{NaNO}_2]{\text{Aq.CH}_3\text{CO}_2\text{H}}$$

CH$_2$NH$_2$
LXXIX

CH$_2$OH

CH$_2$CH$_2$CH$_2$NH$_2$
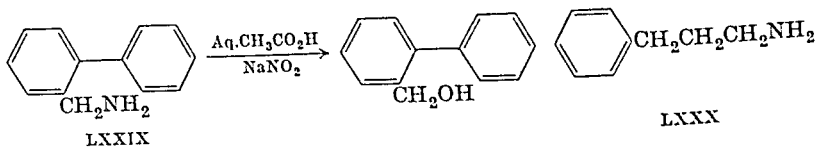
LXXX

(LXXX) does not seem to give any indane.[80] However, a very interesting ring closure involving 2-(2'-naphthyl)diazoacetophenone (LXXXI) to give 6-chrysenol (LXXXII) has been reported by Cook and Schoental.[81]

$$\xrightarrow[\text{in CH}_3\text{CO}_2\text{H}]{\text{10\% H}_2\text{SO}_4}$$

N$_2$CH
LXXXI

OH
LXXXII
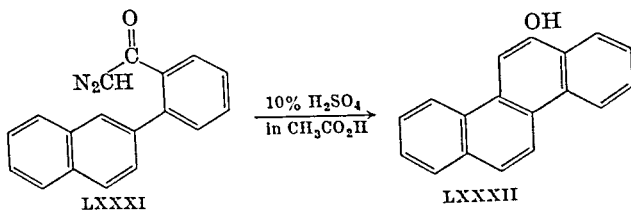
This reaction almost surely involves an intermediate aliphatic diazonium salt.

EXPERIMENTAL CONDITIONS

Preparation of the Amines

The most troublesome aspect of most of the diazonium cyclization reactions is the preparation of the amine having the desired structure. Each of the different types of bridge systems requires a separate approach.

Pschorr Reaction Intermediates. The cinnamic acids required for the Pschorr reaction are generally obtained by a Perkin condensation

CHO
NO$_2$

+

CH$_2$CO$_2$H

$$\xrightarrow[\substack{\text{K}_2\text{CO}_3 \text{ or (C}_2\text{H}_5)_3\text{N} \\ 110°, 8 \text{ hr.}}]{(\text{CH}_3\text{CO})_2\text{O}}$$

CO$_2$H
NO$_2$

LXXXIII
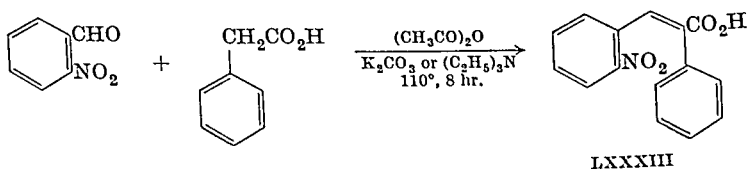
[79] Geissman and Tess, *J. Am. Chem. Soc.*, **62**, 514 (1940).
[80] Fort and Roberts, *J. Am. Chem. Soc.*, **78**, 584 (1956).
[81] Cook and Schoental, *J. Chem. Soc.*, **1945**, 288.

using o-nitrobenzaldehyde or a substituted o-nitrobenzaldehyde. The reaction is illustrated by the preparation of *trans*-2-nitro-α-phenylcinnamic acid (LXXXIII).[32,82]

Pschorr originally specified the use of fused zinc chloride in this reaction, but its presence appears to be detrimental[83] although many succeeding workers have followed the original procedure. For the condensation of o-nitrobenzaldehyde with phenylacetic acid, potassium carbonate proved a more convenient catalyst than potassium phenylacetate, and it gave the same yield. Small amounts of acetic acid or moisture had no effect on the yield.

Fortunately, the presence of the carboxyl group leads to the formation of more of the *trans*-cinnamic acid with the aryl groups in the proper *cis* relationship than of its undesired stereoisomer. A discussion of the preparation of the o-nitrobenzaldehydes and of the phenylacetic acid derivatives is beyond the scope of this chapter. Examples of such preparations are available in many of the references cited in Table I.

A few nitrocinnamic acids such as LXXXIV have been prepared from
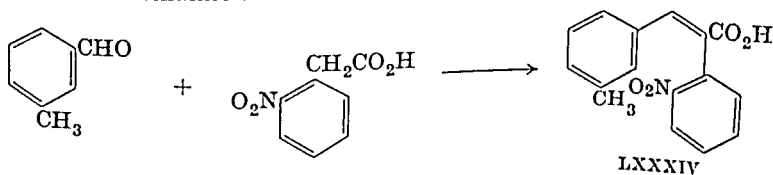
o-nitrophenylacetic acid,[70] which is readily available from o-nitrotoluene. Condensation of o-nitrotoluene with diethyl oxalate in the presence of sodium methoxide followed by hydrolysis gives o-nitrophenylpyruvic acid, which is readily oxidized to o-nitrophenylacetic acid with hydrogen peroxide.[84]

The most satisfactory reducing agent for the nitro group is an ammoniacal suspension of ferrous hydroxide. The hydrated iron oxides are readily removed. Catalytic hydrogenation is difficult to control and often leads to partial reduction of the ethylenic bond.

Some of the amino acids exhibit an interesting polymorphism.[4,84a] Crystallization of *trans*-2-amino-α-phenylcinnamic acid from ethyl acetate leads to a bright yellow modification, m. p. 186–187°, whereas crystallization from ethanol gives colorless prisms sintering at 170° to give the yellow form which then melts at 185–187°.

Several *cis*-stilbene derivatives have been obtained by decarboxylating the cinnamic acid derivatives using the copper chromite hydrogenation

[82] DeTar, *Org. Syntheses*, **35**, 89 (1955).
[83] Bogert and Stamatoff, *Rec. trav. chim.*, **52**, 584 (1933).
[84] May and Mossetig, *J. Org. Chem.*, **11**, 435 (1946).
[84a] Gulland and Virden, *J. Chem. Soc.*, **1928**, 1478.

catalyst in refluxing quinoline.[32,42,85] Rearrangement to the *trans* isomer occurs to only a relatively minor extent during the decarboxylation.

Intermediates for Dihydrophenanthrenes. Catalytic reduction of the 2-nitro-α-phenylcinnamic acids leads to the formation of *sym*-2-aminodiphenylethane derivatives. Another method utilizes the condensation of *p*-methoxybenzaldehyde with oxindole, followed by catalytic

$$CH_3O\text{—C}_6H_4\text{—}CHO + CH_2\text{—}CO\text{—}NH \longrightarrow CH_3O\text{—...} \xrightarrow{H_2, Pd}$$
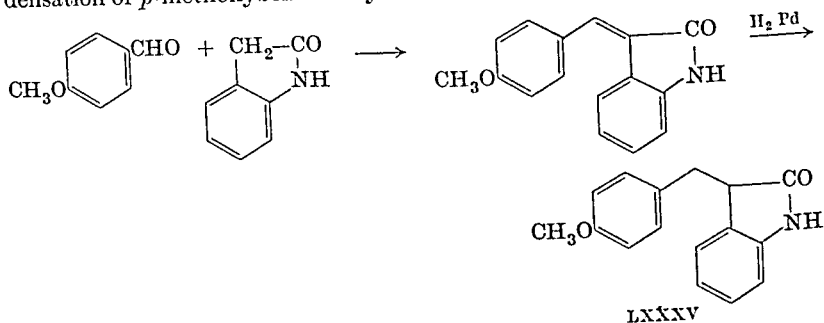
LXXXV

reduction to give 3-(4'-methoxybenzyl)oxindole (LXXXV). The oxindole LXXXV can be hydrolyzed by aqueous barium hydroxide at 170–180°, to give α-(2-aminophenyl)-β-(4'-methoxyphenyl)propionic acid.[86] A third synthesis utilizes the condensation of a benzyl chloride with a phenylacetonitrile as in the preparation of LXXXVI.[87] The nitro

$$CH_3O\text{...}CH_2Cl + O_2N\text{...}CH_2CN\text{...}OCH_3 \xrightarrow[C_2H_5OH]{C_2H_5ONa} CH_3O\text{...}CN\text{...}NO_2$$

LXXXVI
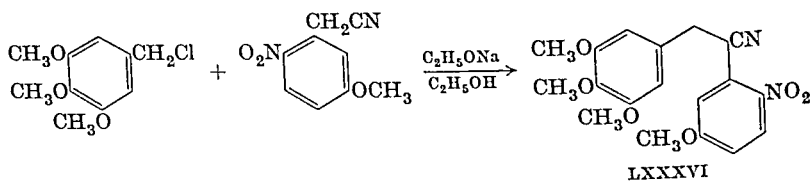
compound was reduced catalytically with 2% palladium on strontium carbonate in dioxane solution.

Intermediates for Fluoranthenes. The required 1-(2'-nitrophenyl)-naphthalene is usually obtained by a mixed Ullmann biaryl synthesis, as

$$\text{naphthyl—I} + Br\text{—}C_6H_3(CH_3)(NO_2) \xrightarrow[150°]{Cu} \text{naphthyl—C}_6H_3(CH_3)(NO_2)$$

LXXXVII
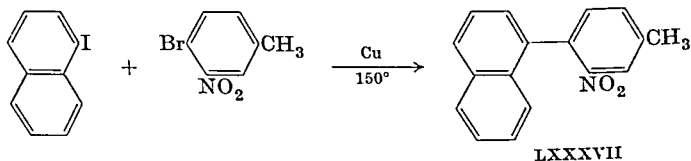
[85] DeTar and Carpino, *J. Am. Chem. Soc.*, **78**, 475 (1956).

[86] Windaus and Eickel, *Ber.*, **57**, 1871 (1924). Compare, Kirchner, *Nachr. Akad. Wiss. Göttingen*, 1921, 154 (*Chem. Zentr.*, **1923**, I, 944).

[87] Cook, Dickson, Ellis and Loudon, *J. Chem. Soc.*, **1949**, 1074.

illustrated for the preparation of 1-(2'-nitro-4'-methylphenyl)naphthalene (LXXXVII); this product was isolated by a combination of distillation and chromatography and was hydrogenated catalytically using Raney nickel.[88]

Intermediates for the Preparation of N-Substituted Carbazoles and Dibenzofurans. The required 2-aminodiphenylamine or 2-amino-diphenyl ether is obtained by either catalytic or chemical reduction of the corresponding nitro compound,[30,89] the latter being obtained from an appropriate o-chloro- or o-bromo-nitrobenzene by reaction with an
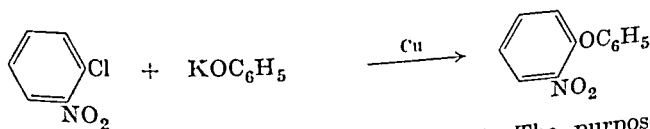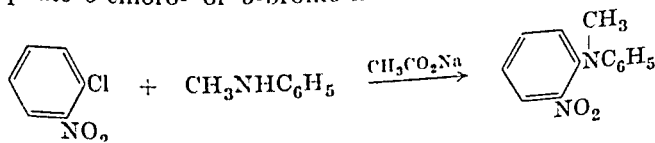
aniline derivative[47] or with a phenolate salt.[90] The purpose of the copper powder in the 2-nitrodiphenyl ether preparation is less that of a catalyst than of an inhibitor. In the absence of the copper, an exothermic reaction takes place leading to a black resin, due perhaps to oxidation of the phenol by the nitro compound.

Intermediates for Fluorenones. The preparation of 2-amino-benzophenones has been reviewed.[91] One useful method starts with anthranilic acid.[92] The amino group is protected with a p-toluenesulfonyl group, and then a Friedel-Crafts synthesis is carried out on the carboxyl group, and then a Friedel-Crafts synthesis is carried out on the carboxyl function as illustrated in the preparation of LXXXVIII. The protective p-toluenesulfonyl group is removed by acid hydrolysis. By this procedure

LXXXVIII
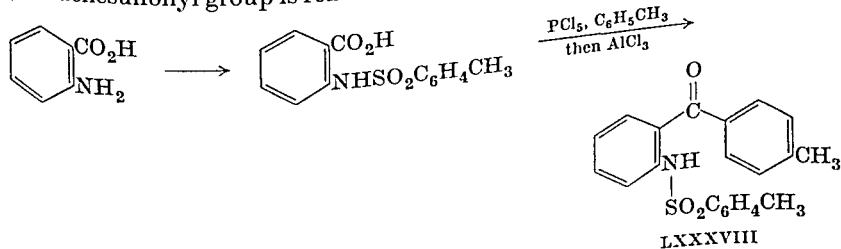
[88] Tucker and Whalley, *J. Chem. Soc.*, **1949**, 3213.
[89] Gilman and Broadbent, *J. Am. Chem. Soc.*, **69**, 2053 (1947).
[90] Brewster and Groening, *Org. Syntheses Coll. Vol. 2*, p. 445 (1943).
[91] Simpson, Atkinson, Schofield, and Stephenson, *J. Chem. Soc.*, **1945**, 646.
[92] Ullmann and Bleier, *Ber.*, **35**, 4273 (1902).

2-aminobenzophenone and 2-amino-4′-methylbenzophenone are obtained in a 50% over-all yield from anthranilic acid.[93]

Unfortunately o-nitrobenzoyl chloride gives very poor yields in Friedel-Crafts reactions.[54] o-Chlorobenzoyl chloride reacts normally, but ammonolysis of the halogen is difficult.[94] On the other hand the o-carboxyl group of o-benzoylbenzoic acids can usually be converted to an amino group via the Hofmann or the Curtius reaction.[95,96]

An interesting oxidation of indole derivatives obtained from phenyl-

hydrazones by the Fischer indole synthesis makes available a number of hitherto inaccessible 2-aminobenzophenones.[94]
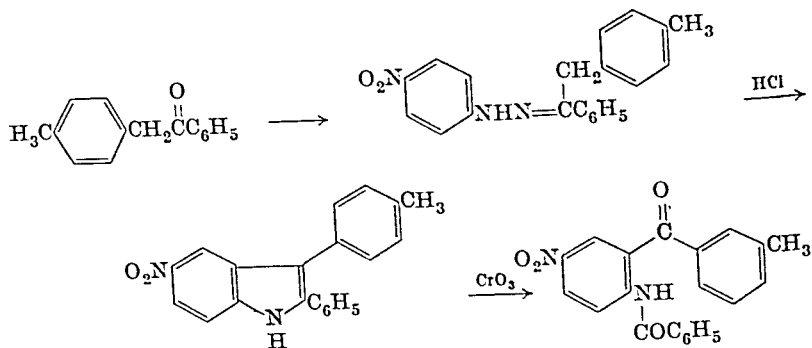
The Cyclization Reaction

The amine is usually diazotized in aqueous sulfuric acid. Insoluble or unreactive amines have been diazotized in acetic acid, methanol, or ethanol with butyl nitrite and sulfuric acid or hydrochloric acid. Amino acids are often dissolved in alkaline solutions along with sodium nitrite, the mixture being run into sulfuric acid.

The numerous methods for bringing about cyclization by decomposition of the diazonium salt fall into a relatively few classes. Although some comparative quantitative data are available on the efficiency of these cyclization procedures, it is necessary in most cases to rely on the evaluation of semiquantitative preparative runs.

Method 1. The diazonium salt solution is merely heated. This procedure nearly always gives some of the cyclization product if cyclization

[93] DeTar and Scheifele, Org. Syntheses, 32, 8 (1952).
[94] Schofield and Theobald, J. Chem. Soc., 1950, 1505.
[95] Graebe and Ullmann, Ann., 291, 8 (1896).
[96] Wallis and Lane, in Adams, Organic Reactions, Vol. III, 267, John Wiley & Sons, New York, 1946; Smith, ibid., 337.

is structurally possible. In the fluorenone series the use of 50% sulfuric acid gives somewhat better yields of the fluorenone and less of the hydroxybenzophenone than does 1 N sulfuric acid.[97] Concentrations of sulfuric acid greater than 75% tend to give lower yields of 3-methylfluorenone, probably because of sulfonation (however, cf. the preparation of 2-nitrofluorenone below, p. 438). For the production of phenanthrene this method is definitely inferior to Method 2 using copper powder.[32]

Method 2. The diazonium salt solution is heated in the presence of copper powder. Gattermann copper[98] prepared by reducing cupric sulfate with zinc dust has been used frequently, though other types of copper may be as good or better. The use of copper powder in the presence of alcoholic solvents is inadvisable except for the phenanthrene cyclization. In other systems the procedure leads to extensive replacement of the diazonium group by hydrogen.

For 2-(4'-methylbenzoyl)benzenediazonium salts, thermal decomposition in 1 N sulfuric acid gave 65% of 3-methylfluorenone, while copper powder in 1 N sulfuric acid gave a 50% yield and led to the formation of some 4-methylbenzophenone. In 50% sulfuric acid an 80% yield of cyclic product was produced whether or not copper or solid cuprous chloride was present. On the other hand 2-(3'-nitrobenzoyl)benzenediazonium salts gave a 35% yield of cyclic product in 1 N sulfuric acid and a 55% yield in 50% sulfuric acid, but with copper powder present a 95% yield of cyclic product was formed in 1 N sulfuric acid and an 85% yield in 50% sulfuric acid. From 2 to 5% of 3-nitrobenzophenone was also produced when copper powder was present. The above results were obtained with crystalline diazonium salts and are based on quantitative chromatographic isolation of the fluorenone-benzophenone mixtures, these being analyzed by their infrared absorption spectra.[97]

Method 3. The diazonium salt solution is made alkaline and heated. In most cases this method gives poor results. It has been used successfully with some Pschorr cyclizations and may have particular merit if there is a hydroxyl group ortho to the diazonium group (resulting in the formation of a relatively stable diazo oxide rather than a diazonium salt).

Method 4. The diazonium salt solution is treated with sodium hypophosphite and copper. This procedure is usable only with the Pschorr cyclization. In all other cases it leads to replacement of the diazonium group by hydrogen. This procedure was first described by Ruggli and Staub[42] and appears to have become fashionable, although there does not appear to be any information about its merit in comparison with Method 2.

[97] DeTar and Whiteley, *J. Am. Chem. Soc.*, **79**, in press (1957).
[98] Gattermann, *Ber.*, **23**, 1219 (1890).

Other Methods. In a few examples the crystalline fluoborate has been suspended in acetone and stirred with copper powder.[25] The method may prove to be of advantage in some cases, but the reported high yields are mostly based on the fluoborate. Yields calculated on the basis of the amine are less attractive.

Another method consists of reaction of the diazonium salt with dimethylamine to give a triazine. The triazine is suspended in an organic solvent and treated with hydrogen chloride. The reported examples seem to give relatively poor yields.[25]

The N-nitrosoamide decomposes on heating to give some cyclization product.[25,98a] This method also seems to be of no particular preparative use.

EXPERIMENTAL PROCEDURES

1-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic Acid. (Pschorr synthesis using Gattermann copper paste[98] in an aqueous acidic medium.)[99]

(a) *Preparation of the amine,* trans-2-*amino*-6-*bromo*-3,4-*dimethoxy-α-phenylcinnamic acid.* A mixture of 15 g. of 6-bromo-3,4-dimethoxy-2-nitrobenzaldehyde (6-bromo-2-nitroveratraldehyde), 8.3 g. of dry sodium phenylacetate, and 90 ml. of acetic anhydride is heated at 100° for thirty hours. Water (750 ml.) is added and, after hydrolysis of the excess anhydride, an excess of ammonia is added and the mixture extracted with two 400-ml. portions of ether. Acidification of the aqueous layer gives 13 g. of the crude nitrocinnamic acid which gives 10.7 g. of material, m. p. 193–200° after one crystallization from methanol. Recrystallization of the combined products of several runs gives the pure nitrocinnamic acid, m. p. 206–208° (30% yield). Reduction with ammoniacal ferrous sulfate gives the aminocinnamic acid in 98% yield.

(b) *Cyclization.* To a mixture of 2 g. of *trans*-2-amino-6-bromo-3,4-dimethoxy-α-phenylcinnamic acid, 20 ml. of ethanol, and 5.2 ml. of 3 N hydrochloric acid is added at 0° a 50% solution of butyl nitrite in ethanol. After one-half hour, the orange solution is diluted with 200 ml. of water, and copper paste is added in small portions with mechanical stirring.* The mixture consisting of light green solution, copper powder, and a white solid, is extracted with ether. Sodium carbonate extraction of the ether followed by acidification of the extract gives 1.57 g. of 1-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid. The yield of partly purified product from several runs was 72–82%. After washing

[98a] DeTar and Savat, *J. Am. Chem. Soc.,* **75,** 7117 (1953).

[99] Small and Turnbull, *J. Am. Chem. Soc.,* **59,** 1541 (1937).

* The quantity of copper paste is not specified in the original article, but the writer has found that quantities of the order of one gram are satisfactory.

with acetone followed by several recrystallizations from ethanol and from acetic acid, the product melts at 260–270° (evac. tube).

4,6-Dimethylphenanthrene-9-carboxylic Acid. (Pschorr synthesis using 75% ethanol as the solvent with copper and sodium hypophosphite as promoters.)[73]

(a) *Preparation of the amine,* trans-2-amino-3-methyl-α-(4'-methylphenyl)cinnamic acid. A mixture of 37.6 g. (0.2 mole) of potassium p-methylphenylacetate, 33 g. (0.2 mole) of 2-nitro-3-methylbenzaldehyde, and 204 g. (2 moles) of acetic anhydride is heated with stirring for eight hours at 105–110°. The anhydride is decomposed at 100° by careful addition of water, and the reaction mixture is poured into 1 l. of cold water, and 5% hydrochloric acid. The solid is recrystallized from acetic acid and then from ethanol to give 38 g. (65%) of the nitrocinnamic acid, m. p. 250.5–251.5°. A suspension of 36 g. of the nitro acid in 500 ml. of warm dilute aqueous ammonia is stirred into a boiling mixture of 240 g. of hydrated ferrous sulfate, 500 ml. of water, and 500 ml. of 12 M aqueous ammonia. Boiling is continued for an hour, and the mixture is allowed to stand overnight. The filtrate from the hydrated iron oxides is acidified to Congo Red with hydrochloric acid. The resulting crude amino acid is recrystallized from 70% methanol to give 27.2 g. (84%) of product, m. p. 176.5–177.5°.

(b) *Cyclization.* A suspension of 15 g. of trans-2-amino-3-methyl-α-(4'-methylphenyl)cinnamic acid in 150 ml. of 15% ethanolic hydrogen chloride is stirred for an hour at 0°, then 20 ml. of freshly distilled amyl nitrite is added and stirring continued for another hour. The solution is then added to a suspension of 1 g. of copper powder in a solution of 50 g. of sodium hypophosphite in 50 ml. of water containing 2 drops of concentrated sulfuric acid. A violent evolution of nitrogen occurs, and the phenanthroic acid separates. After stirring for thirty minutes with gentle heating, the solution is cooled and the acid collected and dissolved in sodium hydroxide solution. The filtered alkaline solution is acidified and the 4,6-dimethyl-9-phenanthroic acid is recrystallized from 80% methanol, using decolorizing carbon (Norit), to give 10 g. (71%) of fine colorless needles, m. p. 216–217°.

3-Chlorophenanthrene-9-carboxylic Acid. (Pschorr reaction via o-nitrophenylacetic acid; cyclization with copper powder in aqueous ethanol.)[84]

(a) *Preparation of the amine,* trans-4-chloro-α-(2'-aminophenyl)cinnamic acid. A mixture of 28 g. of sodium o-nitrophenylacetate, 19 g. of p-chlorobenzaldehyde, 2.5 g. of fused zinc chloride, and 100 ml. of acetic anhydride is heated on the steam bath for twenty hours. Excess anhydride is hydrolyzed, and the crude product is precipitated with water and

recrystallized from acetic acid to give the nitrocinnamic acid; 14.9 g., m. p. 196–199°. For reduction, 5.1 g. of the nitrocinnamic acid is dissolved in 50 ml. of 4 M aqueous ammonia and added to a hot (80–90°) slurry prepared by addition of 85 ml. of 12 M aqueous ammonia to a solution of 34 g. of ferrous sulfate in 102 ml. of water. After ten minutes the mixture is filtered through diatomaceous silica (Filter-Cel). Acidification gives 3.4 g. of the aminocinnamic acid. Attempted crystallization from ethanol gives the lactam, 4-chlorobenzaloxindole.

(b) *Cyclization.* To 80 ml. of 5 N sulfuric acid cooled to −3 to +2° is added during twenty minutes a suspension of 5 g. of *trans*-4-chloro-α-(2'-aminophenyl)cinnamic acid, 3 g. of sodium nitrite, 75 ml. of water, and 2 ml. of M aqueous ammonia. After an additional hour of stirring at 0 to 5°, 20–30 ml. of ethanol and 5 g. of copper-bronze are added, and the mixture is heated to 70–80° for one-half hour. The precipitate is collected on a filter and the alkali-soluble material leached from the copper with hot dilute sodium hydroxide. The alkaline filtrate on acidification gives crude 3-chlorophenanthrene-9-carboxylic acid, which on recrystallization from glacial acetic acid has a m. p. of 249–251°; yield 1.4 g.

2-Nitrofluorenone. (Fluorenone cyclization in concentrated sulfuric acid.)[100] To a solution of 3 g. of 2-amino-5-nitrobenzophenone in 30 ml. of concentrated sulfuric acid, 1 g. of powdered sodium nitrite is added over a period of fifteen minutes at −5 to 0°. The solution is heated at 95° for two hours, then diluted with 60 ml. of water. The product on recrystallization from ethanol gives 1.7 g. (60%) of 2-nitrofluorenone, m. p. 220–221°, and 0.4 g. (13%) of 2-hydroxy-5-nitrobenzophenone, m. p. 119–121°.

With 85% sulfuric acid the yields are 56 and 16%, respectively; with 50% sulfuric acid and copper powder the yields are 15 and 6%.

11-Chrysofluorenone (LXXXIX). (Fluorenone synthesis, use of copper powder; diazotization with isoamyl nitrite.)[101]
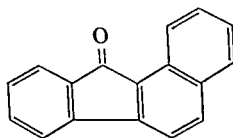
LXXXIX

[100] Nunn, Schofield, and Theobald, *J. Chem. Soc.*, **1952**, 2797.
[101] Orchin and Reggel, *J. Am. Chem. Soc.*, **73**, 436 (1951). The authors give extensive details.

(a) *Preparation of the amine, 1-benzoyl-2-aminonaphthalene.* 1-Benzoyl-2-benzoylaminonaphthalene is prepared from 99 g. of 2-benzoylaminonaphthalene and 160 ml. of benzoyl chloride at a temperature of 100–110°, adding 234 g. of stannic chloride as condensing agent during thirty minutes. The total reaction time is forty-five minutes. After hydrolysis, the product is isolated by crystallization from ethanol. A total of 104 g. (74%) of tan material, m. p. 155–157°, is obtained. 1-Benzoyl-2-aminonaphthalene is obtained in 93% yield by hydrolysis with potassium hydroxide in refluxing 80% ethanol for twelve to sixteen hours.

(b) *Cyclization.* To a stirred solution of 50 g. of 1-benzoyl-2-aminonaphthalene in 1.5 l. of acetic acid containing 21 ml. of sulfuric acid is added in two minutes a solution of 53 ml. of isoamyl nitrite in 250 ml. of acetic acid. After thirty minutes, the solution is cooled in an ice bath and 25.5 g. of copper powder is added; reaction proceeds at ice temperature for thirty minutes, at room temperature for two and one-half hours, and at steam-bath temperature for three hours. The mixture is then allowed to stand overnight. Part of the acetic acid (1.2 l.) is removed by distillation, and the remaining solution is filtered and diluted with water. From the tarry residue, by extraction, distillation, and crystallization, there is obtained 15 g. (33%) of 11-chrysofluorenone, m. p. 133.2–134.8°. No alkali-soluble product is found.

The above procedure has been carried out a number of times with consistent results. Variations in the procedure gave the following results: (a) on addition of copper at room temperature the mixture became hot and the yield dropped to 11%; (b) use of ethanol gave a very low yield; (c) addition of sodium hypophosphite with ethanol or acetic acid as solvent gave very low yields; and (d) use of half as much acetic acid gave a 26% yield.

2-Bromo-4-methyldibenzofuran. (Cyclization by heating acidic solution of diazonium salt.)[102] (a) *Preparation of the amine, 2-amino-4-bromo-6-methyldiphenyl ether.* A mixture of 14.2 g. (0.048 mole) of 2,5-dibromo-3-nitrotoluene and 6.86 g. (0.052 mole) of potassium phenoxide is heated at 170° for three hours. The cooled mixture is treated with water, and the product is extracted with ether and recrystallized from petroleum ether (b. p. 60–68°) to give 12 g. (81%) of phenyl 2-nitro-4-bromo-6-methylphenyl ether, m. p. 92–94°. The nitro group is reduced by dissolving 12 g. (0.039 mole) of the nitro compound in 150 ml. of dry ether to which 20.85 g. (0.093 mole) of stannous chloride has been added, and then saturating the resulting solution with hydrogen chloride at 0°. The hydrochloride separates as a light brown solid (10.9 g.) which is diazotized without further purification.

[102] Gilman, Van Ess, and Hayes, *J. Am. Chem. Soc.*, **61**, 643 (1939).

(b) *Cyclization.* The diazonium solution is added slowly to 150 ml. of boiling 50% sulfuric acid, and the furan steam-distilled to give 4 g. (40% based on the nitro compound) of material, m. p. 106–106.5° after recrystallization from ethanol.

3-Cyanocarbazole. (Example of preparation of a triazine and of a carbazole by thermal decomposition of the triazine.)[103] 2-Nitro-4-cyanodiphenylamine is prepared in 78% yield by heating to the boiling point equimolecular quantities of aniline and of 4-chloro-3-nitrobenzonitrile. Reduction in 78% yield is carried out with stannous chloride in glacial acetic acid and hydrochloric acid. Diazotization yields the triazole in 65% yield. The triazole (1 g.) is heated in a metal bath until nitrogen evolution ceases. Extraction with ethanol and recrystallization from toluene gives 0.3 g. (35%) of 3-cyanocarbazole, m. p. 184–185°.

TABULAR SURVEY OF DIAZONIUM RING CLOSURE REACTIONS

The various examples of the cyclization reaction have been grouped in the following tables according to the type of bridge group involved. The examples are intended to be complete through May, 1956, although by the very nature of the subject some references will certainly have been overlooked. Table IV, which lists a number of examples of carbazole derivatives that have been prepared by heating triazoles, does not aim at completeness.

---

[103] Preston, Tucker, and Cameron, *J. Chem. Soc.*, **1942**, 500.

TABLE I
PHENANTHRENE DERIVATIVES

Product Formula	Starting Amine	Product	Conditions	Yield, %	Reference
$C_{11}H_{10}$	cis-2-Aminostilbene	Phenanthrene	Aq. H_2SO_4	16–42	32
			Aq. H_2SO_4, Cu	60–80	32, 42
			C_2H_5OH, H_2SO_4, Cu	65	42
			Aq. H_2SO_4, NaH_2PO_2, Na_2CO_3	—	104
			Aq. H_2SO_4, NaH_2PO_2, Cu	80	42
	cis-2,4'-Diaminostilbene	Phenanthrene	C_2H_5OH, H_2SO_4, Cu	18	105
$C_{15}H_8Br_2O_2$	trans-2-Amino-4-bromo-α-(4'-bromophenyl)-cinnamic acid	3,6-Dibromophenanthrene-9-carboxylic acid	Aq. C_2H_5OH, Na_2CO_3, Cu, NaH_2PO_2	70–90 crude	106
$C_{23}H_4Cl_2O_2$	trans-2-Amino-α-(3',4'-dichlorophenyl)cinnamic acid	5,6- and 6,7-Dichlorophenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu, NaH_2PO_2	75 crude	107
$C_{15}H_9BrO_2$	trans-2-Amino-α-(2'-bromophenyl)cinnamic acid	8-Bromophenanthrene-9-carboxylic acid	C_2H_5OH, HCl, Cu	50–60	20
	trans-2-Amino-α-(4'-bromophenyl)cinnamic acid	6-Bromophenanthrene-9-carboxylic acid	Aq. H_2SO_4	—	15, 108
$C_{15}H_9ClO_2$	trans-2-Amino-5-chloro-α-phenylcinnamic acid	2-Chlorophenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	65	108
	trans-4-Chloro-α-(2'-aminophenyl)cinnamic acid	3-Chlorophenanthrene-9-carboxylic acid	Aq. C_2H_5OH, H_2SO_4, Cu	30	84
	trans-2-Amino-α-(4'-chlorophenyl)cinnamic acid	6-Chlorophenanthrene-9-carboxylic acid	Aq. H_2SO_4	28	109, 110
$C_{15}H_9NO$	3-(2'-Aminobenzylidene)oxindole	Lactam of 8-aminophenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	58	15
			Aq. H_2SO_4, Cu	75	15
$C_{15}H_9NO_4$	trans-2-Amino-α-(2'-nitrophenyl)cinnamic acid	8-Nitrophenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	24	111
			Acetone, Cu	57	
$C_{15}H_{10}O_2$	trans-2-Amino-α-phenylcinnamic acid	Phenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	93 crude	4, 25
			Aq. H_2SO_4, Cu	86	47
			Aq. HCl, Cu bronze	40	25
			Aq. H_2SO_4	60	47
			Aq. pH 5	57	25
			Aq. pH 7	75	47
			Dry, acetone, Cu*	81	25
			Dry, acetone, Cu*	94	47
			Nitrosoamide, C_6H_6	43	25
			Nitrosoamide, $(C_2H_5)_2O$	37	25
			Triazene†	58	25
	trans-2-Amino-α-(4'-aminophenyl)cinnamic acid	Phenanthrene-9-carboxylic acid	Aq. C_2H_5OH, H_2SO_4, Cu	18	105

* The crystalline diazonium chloride was used, and the yield is based on the diazonium salt.
† The triazene was obtained by coupling the diazonium salt with dimethylamine.

TABLE I—Continued

PHENANTHRENE DERIVATIVES

Product Formula	Starting Amine	Product	Conditions	Yield, %	Reference
$C_{15}H_{10}O_3$	trans-2-Amino-5-hydroxy-α-phenylcinnamic acid	2-Hydroxyphenanthrene-9-carboxylic acid	Aq. NaOH	55	15
$C_{16}H_8O_3$	trans-2-Amino-α-(2'-carboxyphenyl)cinnamic acid	Anhydride of phenanthrene-8,9-dicarboxylic acid	Aq. acid	40–45	15
$C_{16}H_9NO_2$	trans-2-Amino-α-(4'-cyanophenyl)cinnamic acid	6-Cyanophenanthrene-9-carboxylic acid	Aq. H₂SO₄, Cu	58	111
$C_{16}H_{10}O_4$	trans-2-Amino-α-(4'-carboxyphenyl)cinnamic acid	Phenanthrene-6,9-dicarboxylic acid	Aq. H₂SO₄, Cu	48	111
		2,3-Methylenedioxyphenanthrene-9-carboxylic acid	Aq. C₂H₅OH, H₂SO₄, Cu	85	112, 113
	trans-2-Amino-4,5-methylenedioxy-α-phenylcinnamic acid				
$C_{16}H_{12}O_2$	trans-2-Amino-5-methyl-α-phenylcinnamic acid	2-Methylphenanthrene-9-carboxylic acid	Aq. H₂SO₄	75 crude	70
	trans-2-Amino-3-methyl-α-phenylcinnamic acid	4-Methylphenanthrene-9-carboxylic acid	Aq. H₂SO₄	75 crude	70
	trans-2-Amino-α-(4'-methylphenyl)cinnamic acid	6-Methylphenanthrene-9-carboxylic acid	Aq. H₂SO₄, Cu	20	15
		7-Methylphenanthrene-9-carboxylic acid	Na₂CO₃	20	70
			HCl, C₂H₅OH, Cu	70	15
	trans-α-(2'-Amino-5'-methylphenyl)cinnamic acid	8-Methylphenanthrene-9-carboxylic acid	Aq. H₂SO₄	3	70
	trans-2-Amino-α-(2'-methylphenyl)cinnamic acid	2- and 4-Methylphenanthrene-9-carboxylic	Aq. H₂SO₄, Cu	60–70	15
	trans-3-Methyl-α-(2'-aminophenyl)cinnamic acid	acid	Aq. H₂SO₄, Cu		70
		7- and 5-Methylphenanthrene-9-carboxylic acid	Aq. H₂SO₄	—	70
	trans-2-Amino-α-(3'-methylphenyl)cinnamic acid	2-Methoxyphenanthrene-9-carboxylic acid	Na₂CO₃	80	10
$C_{16}H_{12}O_3$	trans-2-Amino-5-methoxy-α-phenylcinnamic acid	4-Methoxyphenanthrene-9-carboxylic acid	H₂SO₄, Cu	Quant.	8
	trans-2-Amino-3-methoxy-α-phenylcinnamic acid	6-Methoxyphenanthrene-9-carboxylic acid	H₂SO₄, Cu	50	5
	trans-2-Amino-α-(4'-methoxyphenyl)cinnamic acid				
	trans-2-Amino-α-(2'-methoxyphenyl)cinnamic acid	8-Methoxyphenanthrene-9-carboxylic acid	H₂SO₄, Cu	55	5
$C_{16}H_{12}O_4$	trans-2-Amino-3-methoxy-4-hydroxy-α-phenylcinnamic acid	3-Hydroxy-1-methoxyphenanthrene-9-carboxylic acid	H₂SO₄, Cu	ca. 3	7
	trans-2-Amino-3-hydroxy-4-methoxy-α-phenylcinnamic acid	1-Hydroxy-3-methoxyphenanthrene-9-carboxylic acid	NaOH	60 crude	13
$C_{17}H_{11}BrO_5$	trans-2-Amino-3-methoxy-α-(2'-bromo-4',5'-methylenedioxyphenyl)cinnamic acid	8-Bromo-4-methoxy-5,6-methylenedioxy-phenanthrene-9-carboxylic acid	Aq. CH₃OH, H₂SO₄, Cu	57	72
$C_{17}H_{12}O_5$	trans-2-Amino-3-methoxy-α-(3',4'-methylenedioxyphenyl)cinnamic acid	4-Methoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid	H₂SO₄, Cu	—	72

Molecular formula	Amino acid	Phenanthrene acid	Conditions	Yield (%)	References
$C_{17}H_{13}BrO_4$	trans-2-Amino-3,4-dimethoxy-6-bromo-α-phenylcinnamic acid	1-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu	70–80	99
	trans-2-Amino-3,4-dimethoxy-5-bromo-α-phenylcinnamic acid	2-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid	C_2H_5OH, HCl, Cu	95 crude	99
	trans-2-Amino-3,4-dimethoxy-α-(2'-bromophenyl)cinnamic acid	8-Bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu	60	15
	trans-2-Amino-α-(2'-bromo-4',5'-dimethoxyphenyl)cinnamic acid	8-Bromo-5,6-dimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	60–65	19, 99
$C_{17}H_{13}ClO_4$	trans-2-Amino-4,5-dimethoxy-α-(4'-chlorophenyl)cinnamic acid	6-Chloro-2,3-dimethoxyphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, H_2SO_4, Cu	35	115
$C_{17}H_{14}O_2$	trans-2-Amino-3-methyl-α-(4'-methylphenyl)cinnamic acid	4,6-Dimethylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu, NaH_2PO_2	71	73
	trans-2-Amino-α-(2',5'-dimethylphenyl)cinnamic acid	5,8-Dimethylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu	85 crude	116
	trans-2-Amino-α-(2',4'-dimethylphenyl)cinnamic acid	6,8-Dimethylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu	87 crude	83
	trans-2-Amino-α-(3'-ethylphenyl)cinnamic acid	5- and 7-Ethylphenanthrene-9-carboxylic acid	H_2SO_4, Cu	95	117
	trans-2-Amino-α-(4'-ethylphenyl)cinnamic acid	6-Ethylphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	40	83
$C_{17}H_{14}O_3$	trans-2-Amino-3-methoxy-α-(2'-methylphenyl)cinnamic acid	4-Methoxy-8-methylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu; NaOH	80 crude; 43	118
	trans-2-Amino-α-(5'-methoxy-2'-methylphenyl)cinnamic acid	5-Methoxy-8-methylphenanthrene-9-carboxylic acid	CH_3OH, H_2SO_4	—	119
	trans-2-Amino-α-(4'-methoxy-2'-methylphenyl)cinnamic acid	6-Methoxy-8-methylphenanthrene-9-carboxylic acid	NaOH	—	120
	trans-2-Amino-α-(2'-methoxy-3-methylphenyl)cinnamic acid	5-Methoxy-7-methylphenanthrene-9-carboxylic acid	Na_2CO_3, Cu	—	62
	trans-2-Amino-α-(4'-ethoxyphenyl)cinnamic acid	6-Ethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	50–60	114
$C_{17}H_{14}O_4$	trans-2-Amino-4,5-dimethoxy-α-phenylcinnamic acid	2,3-Dimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	70–80	9
	trans-2-Amino-3,4-dimethoxy-α-phenylcinnamic acid	3,4-Dimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	80	7
	trans-2-Amino-α-(3,4-dimethoxyphenyl)cinnamic acid	6,7-Dimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4	60	121, 122
	trans-2-Amino-5-methoxy-α-(3'-methoxyphenyl)cinnamic acid	2,5-Dimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4	35	19
	trans-2-Amino-5-methoxy-α-(3'-methoxyphenyl)cinnamic acid	2,7-Dimethoxyphenanthrene-9-carboxylic acid	Aq. Na_2CO_3	28	123

TABLE I—Continued
PHENANTHRENE DERIVATIVES

Product Formula	Starting Amine	Product	Conditions	Yield, %	Reference
$C_{17}H_{14}O_3$	trans-2-Amino-3-hydroxy-4-methoxy-α-(4'-methoxyphenyl)cinnamic acid	3,6-Dimethoxy-4-hydroxyphenanthrene-9-carboxylic acid	Aq. KOH	70	12
	trans-2-Amino-3-methoxy-4-hydroxy-α-(2'-methoxyphenyl)cinnamic acid	4,8-Dimethoxy-3-hydroxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	20–25	6
	trans-2-Amino-3,4-dimethoxy-α-(2'-carboxyphenyl)cinnamic acid	4,5-Dimethoxy-3-methoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4	75	15
$C_{18}H_{12}O_5$	trans-2-Amino-3,4-dimethoxy-α-(2'-carboxyphenyl)cinnamic acid	Anhydride of 3,4-dimethoxyphenanthrene-8,9-dicarboxylic acid	Aq. C_2H_5OH, HCl, Cu	50 crude	124
$C_{18}H_{14}O_4$	trans-2-Amino-4,5-methylenedioxy-α-(2',5'-dimethylphenyl)cinnamic acid	5,8-Dimethyl-2,3-methylenedioxyphenanthrene-9-carboxylic acid		—	125
$C_{19}H_{13}BrO_6$	trans-2-Amino-5,6-dimethoxy-α-(2'-bromo-4',5'-methylenedioxyphenyl)cinnamic acid	4-Bromo-1,2-dimethoxy-5,6-methylenedioxyphenanthrene-9-carboxylic acid		—	125
	trans-2-Amino-4,5-dimethoxy-α-(2'-bromo-4',5'-methylenedioxyphenyl)cinnamic acid	4-Bromo-2,3-dimethoxy-5,6-methylenedioxyphenanthrene-9-carboxylic acid		—	125
$C_{18}H_{14}O_6$	trans-2-Amino-5,6-dimethoxy-α-(3',4'-methylenedioxyphenyl)cinnamic acid	1,2-Dimethoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid and 1,2-dimethoxy-5,6-methylenedioxy-phenanthrene-9-carboxylic acid		—	125
		2,3-Dimethoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid and 2,3-dimethoxy-5,6-methylenedioxyphenanthrene-9-carboxylic acid		—	125
	trans-2-Amino-4,5-dimethoxy-α-(3',4'-methoxyphenyl)cinnamic acid	3,4-Dimethoxy-6,7-methylenedioxyphenanthrene-9-carboxylic acid		—	125
	trans-2-Amino-3,4-dimethoxy-α-(3',4'-methylenedioxyphenyl)cinnamic acid	5-Bromo-3,4,5-trimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4	—	125
$C_{19}H_{15}BrO_5$	trans-2-Amino-3,4-dimethoxy-α-(5'-bromo-2'-methoxyphenyl)cinnamic acid	5-Bromo-3,4-trimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	15–50	20, 127
	trans-2-Amino-3,4-dimethoxy-α-(2'-bromo-5'-methoxyphenyl)cinnamic acid	4-Bromo-3,4,5-trimethoxyphenanthrene-9-carboxylic acid			
$C_{18}H_{16}O_2$	trans-2-Amino-3-methyl-α-(4'-ethylphenyl)cinnamic acid	6-Ethyl-4-methylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu, NaH_2PO_3	58	73
	trans-2-Amino-3-methyl-α-(3'-ethylphenyl)cinnamic acid	7-Ethyl-4-methylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu, NaH_2PO_3	30	73

Formula	Cinnamic acid	Phenanthrene carboxylic acid	Conditions	Yield	References
$C_{18}H_{16}O_4$	trans-2-Anion-3,4-dimethoxy-α-(4'-methyl-phenyl)cinnamic acid	3,4-Dimethoxy-6-methylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu	80	15
	trans-2-Amino-3,4-dimethoxy-α-(2'-methyl-phenyl)cinnamic acid	3,4-Dimethoxy-8-methylphenanthrene-9-carboxylic acid	Aq. Na_2CO_3	90 crude	15
	trans-2-Amino-4-hydroxy-3-methoxy-α-(2',5'-dimethylphenyl)cinnamic acid	5,8-Dimethyl-3-hydroxy-4-methoxy-phenanthrene-9-carboxylic acid	Dioxane, H_2SO_4, Cu, NaH_2PO_2	47 crude	128
$C_{18}H_{16}O_5$	trans-2-Amino-3,4-dimethoxy-α-(4'-methoxy-phenyl)cinnamic acid	3,4,6-Trimethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4	70	12
	trans-2-Amino-3,4-dimethoxy-α-(2'-methoxy-phenyl)cinnamic acid	3,4,8-Trimethoxyphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu	—	16
	trans-2-Amino-3,4-dimethoxy-α-(3'-methoxy-phenyl)cinnamic acid	3,4,5- and 3,4,7-Trimethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4	—	20
$C_{19}H_{12}O_2$	trans-2-Amino-α-(2'-naphthyl)cinnamic acid	Benzo[c]phenanthrene-6-carboxylic acid; Benz[a]anthracene-6-carboxylic acid	Aq. H_2SO_4, Cu	6 / 0.6	76, 120, 130
	trans-2-Amino-α-(1'-naphthyl)cinnamic acid	Chrysene-5-carboxylic acid	Aq. C_2H_5OH, H_2SO_4, Cu, NaH_2PO_2	28	74, 130
$C_{19}H_{17}BrO_6$	trans-2-Amino-3,4-dimethoxy-α-(2'-bromo-4',5'-dimethoxyphenyl)cinnamic acid	8-Bromo-3,4,5,6-tetramethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	27	131, 132
$C_{19}H_{18}O_2$	trans-2-Amino-α-(2',3',4',5'-tetramethylphenyl)cinnamic acid	5,6,7,8-Tetramethylphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	30	133a
	trans-2-Amino-α-(2'-methyl-5'-isopropylphenyl)cinnamic acid	8-Methyl-5-isopropylphenanthrene-9-carboxylic acid	Aq. C_2H_5OH, HCl, Cu	65 crude	83
	trans-2-Amino-α-(2'-methyl-4'-isopropylphenyl)cinnamic acid	6-Isopropyl-8-methylphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	61	133b
$C_{19}H_{18}O_4$	trans-2-Amino-3,4-dimethoxy-α-(2',5'-dimethylphenyl)cinnamic acid	3,4-Dimethoxy-5,8-dimethylphenanthrene-9-carboxylic acid	Dioxane, H_2SO_4, NaH_2PO_2, Cu	50	128
	trans-2-Amino-4,5-dimethoxy-α-(2',5'-dimethylphenyl)cinnamic acid	2,3-Dimethoxy-5,8-dimethylphenanthrene-9-carboxylic acid	Dioxane, H_2SO_4, NaH_2PO_2, Cu	83 crude	134
$C_{19}H_{18}O_5$	trans-2-Amino-3,4-dimethoxy-α-(2'-ethoxy-phenyl)cinnamic acid	8-Ethoxy-3,4-dimethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4	80	17
$C_{19}H_{18}O_6$	trans-2-Amino-3,4,5-trimethoxy-α-(4'-methoxy-phenyl)cinnamic acid	2,3,4,6-Tetramethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4	50	135, 136
	trans-2-Amino-5-methoxy-α-(3',4',5'-trimethoxy-phenyl)cinnamic acid	2,5,6,7-Tetramethoxyphenanthrene-9-carboxylic acid	Aq. dioxane, NaH_2PO_2, Cu, H_2SO_4	63	137
			Aq. Na_2CO_3	—	138

Note: References 104–225 are listed on pp. 400–402.

TABLE I—Continued

PHENANTHRENE DERIVATIVES

Product Formula	Starting Amine	Product	Conditions	Yield, %	Reference
$C_{19}H_{18}O_6$ (Cont.)	trans-2-Amino-3,4-dimethoxy-α-(2',5'-dimethoxyphenyl)cinnamic acid	3,4,5,8-Tetramethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4	50 crude	139
	trans-2-Amino-3,4-dimethoxy-α-(2',4'-dimethoxyphenyl)cinnamic acid	3,4,6,8-Tetramethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4	30	18
	trans-2-Amino-3,4-dimethoxy-α-(2',4'-dimethoxyphenyl)cinnamic acid	2,3,4,7-Tetramethoxyphenanthrene-9-carboxylic acid	Dimethylformamide, H_2SO_4, Cu	65	140
	trans-3,4,5-Trimethoxy-α-(2'-amino-5'-methoxyphenyl)cinnamic acid	2,3,4,5- and 2,3,4,7-Tetramethoxyphenanthrene-9-carboxylic acid	Aq. Na_2CO_3	—	136
	trans-2-Amino-3,4,5-trimethoxy-α-(3'-methoxyphenyl)cinnamic acid	3,4,5,6-Tetramethoxyphenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	0	131, 132
	trans-2-Amino-3,4-dimethoxy-α-(3',4'-dimethoxyphenyl)cinnamic acid	3,4,6,7-Tetramethoxyphenanthrene-9-carboxylic acid		13	
$C_{20}H_{12}O_4$	trans-2-Amino-4,5-methylenedioxy-α-(1'-naphthyl)cinnamic acid	8,9-Methylenedioxychrysene-5-carboxylic acid	Aq. dioxane, C_2H_5OH, H_2SO_4, Cu, NaH_2PO_2	95 crude	141
$C_{20}H_{14}O_3$	trans-2-Amino-5-methoxy-α-(1'-naphthyl)cinnamic acid	8-Methoxychrysene-5-carboxylic acid	Aq. C_2H_5OH, Na_2CO_3	25	81
$C_{20}H_{20}O_5$	trans-2-Amino-3,4-dimethoxy-α-(5'-ethyl-2'-methoxyphenyl)cinnamic acid	5-Ethyl-3,4,8-trimethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4	35	142
$C_{20}H_{20}O_6$	trans-2-Amino-3,4-dimethoxy-α-(4'-ethoxy-2'-methoxyphenyl)cinnamic acid	6-Ethoxy-3,4,7-trimethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4, Cu	35	143
	trans-2-Amino-3,4-dimethoxy-α-(4'-ethoxy-2'-methoxyphenyl)cinnamic acid	6-Ethoxy-3,4,5-trimethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4, Cu	35	143
	trans-2-Amino-3,4-dimethoxy-α-(3'-ethoxy-4'-methoxyphenyl)cinnamic acid	7-Ethoxy-3,4,6-trimethoxyphenanthrene-9-carboxylic acid		13	
	trans-2-Amino-3,4-dimethoxy-α-(3'-ethoxy-4'-methoxyphenyl)cinnamic acid	5-Ethoxy-3,4,6-trimethoxyphenanthrene-9-carboxylic acid	Aq. CH_3OH, H_2SO_4, Cu	35	143
$C_{21}H_{14}O_2$	trans-2-Amino-α-(3'-acenaphthenyl)cinnamic acid	Cholanthrene-12-carboxylic acid	Dioxane, C_2H_5OH, Cu, NaH_2PO_2	5	144
$C_{21}H_{16}O_2$	trans-2-Amino-α-(3',4'-dimethyl-1'-naphthyl)cinnamic acid	11,12-Dimethylchrysene-5-carboxylic acid	Aq. H_2SO_4, Cu	30	145
$C_{21}H_{16}O_4$	trans-2-Amino-3,4-dimethoxy-α-(1'-naphthyl)cinnamic acid	1,2-Dimethoxychrysene-6-carboxylic acid	Aq. (iso C_5H_{11})$_2$O, H_2SO_4, Cu, NaH_2PO_2	95 crude	146

TABLE II

DIHYDROPHENANTHRENE DERIVATIVES

Product Formula	Starting Amine	Product	Conditions	Yield, %	Reference
$C_{13}H_{11}N$	1-(2'-Aminophenyl)-2-(2''-pyridyl)ethane	5,6-Dihydrobenzo[f]quinoline	Aq. dioxane, H_2SO_4, Cu	4	25
			Nitrosoamide	40	25
			Triazene*	0	25
			C_2H_5OH, H_2SO_4, Cu	20	42
$C_{14}H_{12}$	1-(2'-Aminophenyl)-2-phenylethane	9,10-Dihydrophenanthrene	Aq. H_2SO_4, Cu	—	4, 86
$C_{15}H_{12}O_2$	α-Phenyl-1-β-(2-aminophenyl)propionic acid	9,10-Dihydrophenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	—	86
	α-(2-Aminophenyl)-β-phenyl)propionic acid	9,10-Dihydrophenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	20	86
$C_{16}H_{12}O_4$	α-(2-Aminophenyl)-β-(3',4'-methylenedioxy-phenyl)propionic acid	2,3(or 3,4-)Methylenedioxy-9,10-dihydrophenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	15	86
$C_{16}H_{14}O_3$	α-(2-Aminophenyl)-β-(4'-methoxyphenyl)propionic acid	3-Methoxy-9,10-dihydrophenanthrene-9-carboxylic acid	Aq. H_2SO_4, Cu	Small	156
	α-(2-Aminophenyl)-β-phenylbutyric acid	10-Methyl-9,10-dihydrophenanthrene-9-carboxylic acid	Aq. dioxane, HCl, Cu	45	87
$C_{19}H_{19}NO_4$	α-(2-Amino-5-methoxyphenyl)-β-(3',4',5'-trimethoxyphenyl)propionitrile	2,3,4,7-Tetramethoxy-9-cyano-9,10-dihydrophenanthrene	Na_2CO_3 or CH_3CO_2Na	None	

Note: References 104–225 are listed on pp. 460–462.

* The triazene was prepared by coupling the diazonium salt with dimethylamine and was then heated in benzene solution while hydrogen chloride was bubbled in.

TABLE III

FLUORANTHENE DERIVATIVES

Numbering System for Fluoranthene
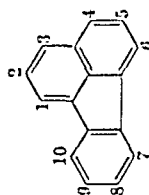
Product Formula	Starting Amine	Product	Conditions	Yield, %	Reference
$C_{16}H_{10}$	1-(2'-Aminophenyl)naphthalene	Fluoranthene	Aq. CH_3CO_2H, H_2SO_4, Cu	48	45
$C_{17}H_{12}$	1-(2'-Amino-6'-methylphenyl)naphthalene	7-Methylfluoranthene	Aq. H_2SO_4, Cu	—	88, 157
	1-(2'-Amino-3'-methylphenyl)naphthalene	7-Methylfluoranthene	Aq. CH_3CO_2H, H_2SO_4	45*	157
	1-(2'-Amino-4'-methylphenyl)naphthalene	8-Methylfluoranthene	Aq. H_2SO_4, Cu	—	88
$C_{17}H_{12}O$	1-(2'-Aminophenyl)-2-methoxynaphthalene	1-Methoxyfluoranthene	Aq. H_2SO_4, Cu	—	158
	1-(2'-Aminophenyl)-4-methoxynaphthalene	3-Methoxyfluoranthene	Aq. H_2SO_4, Cu	48	158
	1-(2'-Methoxyphenyl)-8-aminonaphthalene	7-Methoxyfluoranthene	Aq. H_2SO_4, Cu	—	158
	1-(2'-Amino-4'-methoxyphenyl)naphthalene	8-Methoxyfluoranthene	Aq. CH_3CO_2H, H_2SO_4, Cu	52	159
$C_{18}H_{14}$	1-(2'-Amino-4'-dimethylnaphthalene	1,3-Dimethylfluoranthene	Aq. HCl, Cu	Poor	45
$C_{19}H_{14}O_2$	1-(2'-Aminophenyl)-2,4-dimethylnaphthalene	Ethyl fluoranthene-8-carboxylate	Aq. H_2SO_4, Cu	15	88
$C_{19}H_{16}$	1-(2'-Amino-4'-carbethoxyphenyl)naphthalene	1,2,3-Trimethylfluoranthene	Aq. H_2SO_4, Cu	—	160
$C_{22}H_{12}$	3-(2'-Aminophenyl)-2,3,4-trimethylnaphthalene	Indeno[1,2,3-cd]fluoranthene	Aq. H_2SO_4, Cu	38	161
$C_{23}H_{14}$	4-(2'-Aminophenyl)-1-methylfluoranthene	5-Methylindeno[1,2,3-cd]fluoranthene	Aq. CH_3CO_2H, H_2SO_4, Cu	—	162
	4-(2'-Aminophenyl)-2-methylfluoranthene	5-Methylindeno[1,2,3-cd]fluoranthene	Aq. CH_3CO_2H, H_2SO_4, Cu	—	162

Note: References 104-225 are listed on pp. 400-402.

* The use of copper did not increase the yield.

TABLE IV

CARBAZOLE DERIVATIVES PREPARED VIA TRIAZOLES

Numbering System for Carbazole
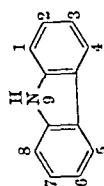
Product Formula	Product Name	References
$C_{11}H_8N_2$	5-Pyrid[4,3-b]indole	103
$C_{12}H_7N_3O_4$	1,3-Dinitrocarbazole	104
$C_{12}H_6ClN$	2-Chlorocarbazole	105
	3-Chlorocarbazole	105, 106
$C_{12}H_8N_2$	2-Aminocarbazole	103
	3-Aminocarbazole	105
$C_{12}H_8N_2O_2$	1-Nitrocarbazole	103
	3-Nitrocarbazole	103
$C_{12}H_9N$	Carbazole	69, 107
$C_{13}H_8N_2$	3-Cyanocarbazole	103
$C_{13}H_9N_3$	1-Methylcarbazole	105
$C_{13}H_{11}N$	3-Methylcarbazole	105
$C_{13}H_{12}N_2$	3-Amino-6-methylcarbazole	103
$C_{14}H_{11}NO$	3-Acetylcarbazole	103
$C_{14}H_{13}N$	1,3-Dimethylcarbazole	165
$C_{12}H_6N_3O_4$	8,10-Dinitro-7-benz[k]acridine	164
$C_{16}H_{11}N$	Benzo[a]carbazole	164
	7-Benz[k]acridine	164
$C_{17}H_{13}N$	10-Methylbenzo[c]carbazole	165
$C_{19}H_{13}NO$	3-Benzoylcarbazole	169
$C_{20}H_{10}BrNO_2$	7-Bromo-12-naphtho[2,3-a]carbazole-5,13-dione	168
$C_{20}H_{11}NO_2$	12-Naphtho[2,3-a]carbazole-5,13-dione	168
$C_{24}H_{16}N_2$	1,1'-Bicarbazole	170
	3,9'-Bicarbazole	171
	3,3'-Bicarbazole	172
$C_{26}H_{17}NO_2$	3,6-Dibenzoylcarbazole	173

Note: References 104–225 are listed on pp. 460–462.

TABLE VI

DIBENZOFURAN DERIVATIVES AND SULFUR ANALOGS
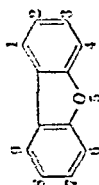
Numbering System for Dibenzofuran

Product Yields	Starting Material	Product	Procedure	Yield, %	Reference
$C_{12}H_6Br_2O$	2-Amino-4',5-dibromodiphenyl ether	2,7-Dibromodibenzofuran	Aq. H_2SO_4	—	176
	2-Amino-4,4'-dibromodiphenyl ether	2,8-Dibromodibenzofuran	Aq. H_2SO_4	—	176
$C_{12}H_6ClNO_3$	2-Amino-4'-chloro-5-nitrodiphenyl ether	2-Chloro-7-nitrodibenzofuran	Aq. H_2SO_4	—	176
$C_{12}H_6Cl_2O$	2-Amino-4,4'-dichlorodiphenyl ether	2,8-Dichlorodibenzofuran	Aq. H_2SO_4	—	176
$C_{12}H_7BrO$	2-Amino-4-bromodiphenyl ether	2-Bromodibenzofuran	Aq. H_2SO_4	—	176
	2-Amino-4'-bromodiphenyl ether	2-Bromodibenzofuran	Aq. H_2SO_4	—	176
	2-Amino-5-bromodiphenyl ether	3-Bromodibenzofuran	Aq. H_2SO_4	—	176
$C_{12}H_7ClO$	2-Amino-4-chlorodiphenyl ether	2-Chlorodibenzofuran	Aq. H_2SO_4	—	176
	2-Amino-4'-chlorodiphenyl ether	2-Chlorodibenzofuran	Aq. H_2SO_4	3	177
	2-Amino-5-chlorodiphenyl ether	3-Chlorodibenzofuran	Aq. H_2SO_4	—	176
$C_{12}H_7NO_3$	2-Amino-5-nitrodiphenyl ether	3-Nitrodibenzofuran	Aq. H_2SO_4	30	178
$C_{12}H_8O$	2-Aminodiphenyl ether	Dibenzofuran	Aq. H_2SO_4	45	30
			Aq. NaOH + CuOH	0	30
			Aq. NaOH	0	30

Formula	Amine	Product	Conditions	Yield	Ref.
$C_{13}H_7BrO_3$	2-Amino-4'-bromo-6-carboxydiphenyl ether	2-Bromodibenzofuran-6-carboxylic acid	Aq. H_2SO_4	15	102
$C_{13}H_9BrO$	2-Amino-4-bromo-6-methyldiphenyl ether	2-Bromo-4-methyldibenzofuran	Aq. H_2SO_4	40	102
$C_{13}H_9BrO_2$	2-Amino-4-bromo-4'-methoxydiphenyl ether	2-Bromo-8-methoxydibenzofuran	Aq. H_2SO_4	8	58
$C_{12}H_7NO_2S$	2-Amino-4-nitrodiphenyl sulfide	2-Nitrodibenzothiophene	Aq. H_2SO_4	20	179
$C_{12}H_8S$	2-Aminodiphenyl sulfide	Dibenzothiophene	Aq. H_2SO_4	40	46
			Aq. H_2SO_4	15	30
			Aq. H_2SO_4, Cu	25–35	30
			Aq. H_2SO_4, $CuSO_4$	25	30
			pH 8–9	10	30
$C_{12}H_8O_2S$	2-Aminodiphenyl sulfone	Dibenzothiophene dioxide	H_2SO_4, $CuSO_4$	5	30
			H_2SO_4, Cu	<30	30
			NaOH	None	30
$C_{12}H_8Se$	2-Aminodiphenyl selenide	Dibenzoselenophene	HCl, Cu	22	180
$C_{13}H_{10}S$	2-Amino-4'-methyldiphenyl sulfide	2-Methyldibenzothiophene	85% H_2SO_4	Trace	46
			Aq. H_2SO_4	22	30
			Aq. H_2SO_4, Cu	23–40	30
$C_{13}H_{10}O_2S$	2-Amino-4'-methyldiphenyl sulfone	2-Methyldibenzothiophene dioxide	Aq. NaOH	None	30
			Aq. H_2SO_4, Cu	3	30
$C_{14}H_{11}NO_3S$	2-Amino-4-nitro-4'-ethoxydiphenyl sulfide	2-Ethoxy-8-nitrodibenzothiophene	Aq. CH_3CO_2H, HCl, Cu	70	181
$C_{14}H_{10}O_2S$	2-Aminophenyl-1'-naphthyl sulfone	Naphtho[1,2-b]thianaphthene-11-dioxide	Aq. CH_3CO_2H, HCl, Cu	32	180
$C_{16}H_{10}S$	2-Aminophenyl-2'-naphthyl sulfone	Naphtho[2,1-b]thianaphthene-7-dioxide	H_2SO_4	Trace	180
	2-Aminophenyl-1'-naphthyl sulfide	Naphtho[1,2-b]thianaphthene	Aq. CH_3CO_2H, HCl, Cu	—	180
	1-Aminophenyl-2-naphthyl sulfide	Naphtho[2,1-b]thianaphthene	Aq. CH_3COOH, HCl, Cu	0	180
			50% H_2SO_4	2	182

Note: References 104–225 are listed on pp. 460–462.

TABLE VII

FLUORENE DERIVATIVES

Formula	Starting Value	Product	Procedure	Yield, %	Reference
$C_{13}H_{12}$	2-Aminodiphenylmethane	Fluorene	Aq. HCl	13	47
			Aq. HCl, Cu	0	47
			$(C_2H_5)_2O$, Cu Acetone, Cu	0	47
			Aq. H_2SO_4	0	1
			Nitrosamide, C_6H_6	—	47
			Aq. H_2SO_4	—	183
$C_{27}H_{25}N_3O_2$	Bis-(4'-dimethylaminophenyl)-2-amino-5-nitrophenylmethane	3,4'-Bis(dimethylamino)-7-nitro-9-phenylfluorene	Aq. H_2SO_4	16	183
$C_{27}H_{26}N_2$	Bis-(4'-dimethylaminophenyl)-2-aminobiphenyl-methane	3,4'-Bis(dimethylamino)-9-phenylfluorene	Aq. H_2SO_4	22	183
$C_{28}H_{28}N_2$	Bis-(4'-dimethylaminophenyl)-2-amino-5-methylphenylmethane	3,4'-Bis(dimethylamino)-7-methyl-9-phenylfluorene	70% H_2SO_4	30	184
$C_{29}H_{31}N_3$	Bis-(4'-dimethylaminophenyl)-2-amino-4-dimethylaminophenylmethane	3,7,4'-Tris(dimethylamino)-9-phenylfluorene			
$C_{31}H_{28}N_2$	Bis-(4'-dimethylaminophenyl)-2-amino-1-naphthylmethane	8,4'-Bis(dimethylamino)-11-phenylbenzo[a]-fluorene	Aq. H_2SO_4	—	183

Note: References 101–225 are listed on pp. 460–462.

TABLE VIII

FLUORENONE DERIVATIVES

Product Formula	Starting Amine	Product	Procedure	Yield, %	Reference
$C_{13}H_6N_2O_5$	2-Amino-3,5-dinitrobenzophenone	2,4-Dinitrofluorenone	Aq. H_2SO_4	78 crude	185
$C_{13}H_7BrO$	2-Amino-6-bromobenzophenone	1-Bromofluorenone	Aq. H_2SO_4	25	186
$C_{13}H_7NO_3$	2-Amino-6-nitrobenzophenone	1-Nitrofluorenone	Aq. H_2SO_4	7	100
	2-Amino-2'-nitrobenzophenone	1-Nitrofluorenone	Aq. H_2SO_4	9	47
			Aq. H_2SO_4, Cu	7	47
			Acetone, Cu	0	47
	2-Amino-5-nitrobenzophenone	2-Nitrofluorenone	Aq. H_2SO_4	55–60	100, 187
			Aq. H_2SO_4, Cu	45	
	2-Amino-4-nitrobenzophenone	3-Nitrofluorenone	Aq. CH_3CO_2Na, Cu	95 crude	100
	2-Amino-3-nitrobenzophenone	4-Nitrofluorenone	Aq. H_2SO_4	48	100
	2-Amino-3'-nitrobenzophenone	2-Nitrofluorenone	Aq. H_2SO_4	20*	31
		4-Nitrofluorenone		15*	
$C_{13}H_8O$	2-Aminobenzophenone	Fluorenone	Aq. H_2SO_4	65*	31
			Aq. H_4SO_4, $CuSO_4$	60*	31
			Aq. H_2SO_4, Cu	71*	31
			pH 9, 12	25*	31
			Acetone, Cu	0	47
			Aq. HCl, H_3PO_2, Cu	0	47
			NH_4OH + Cu	10	30
			NaOH	20	31, 47
$C_{14}H_8N_2O_5$	2-Amino-6-methyl-3,5-dinitrobenzophenone	1-Methyl-2,4-dinitrofluorenone	Aq. H_2SO_4	80	95
	2-Amino-4-methyl-3,5-dinitrobenzophenone	3-Methyl-2,4-dinitrofluorenone	Aq. H_2SO_4	65	188
$C_{14}H_8O_3$	2-Amino-2'-carboxybenzophenone	Fluorene-1-carboxylic acid	Aq. H_2SO_4	50	188
		Fluorene	Aq. H_2SO_4	10	61
				10	

Note: References 104–225 are listed on pp. 460–462.

* These yields are based on the isolated diazonium fluoborate; the other yields in the table are based on the amine.

TABLE VIII—Continued

FLUORENONE DERIVATIVES

Product Formula	Starting Amine	Product	Procedure	Yield, %	Reference
$C_{14}H_9NO_3$	2-Amino-6-methyl-3-nitrobenzophenone	1-Methyl-1-nitrofluorenone	Aq. H₂SO₄	55	188
	2-Amino-4-methyl-5-nitrobenzophenone	3-Methyl-2-nitrofluorenone	Aq. H₂SO₄	60	180
	2-Amino-4'-methyl-5-nitrobenzophenone	3-Methyl-7-nitrofluorenone	Aq. H₂SO₄	75 crude	189
$C_{14}H_{10}O$	2-Amino-2'-methylbenzophenone	1-Methylfluorenone	Aq. HCl	50	75, 102
	2-Amino-3'-methylbenzophenone	2-Methylfluorenone	Aq. HCl	low	75
	2-Amino-4'-methylbenzophenone	3-Methylfluorenone	Aq. H₂SO₄	60*	31, 187, 180
$C_{14}H_{10}O_2$	2-Amino-4'-methoxybenzophenone	3-Methoxyfluorenone	Aq. H₂SO₄	80 crude	92, 100
$C_{15}H_{11}NO_3$	2-Amino-4',6-dimethyl-3-nitrobenzophenone	1,6-Dimethyl-4-nitrofluorenone	Aq. H₂SO₄	55	188
	2-Amino-4',6-dimethyl-5-nitrobenzophenone	3,6-Dimethyl-2-nitrofluorenone	Aq. H₂SO₄	60	101
$C_{15}H_{12}O$	2-Amino-4,4'-dimethylbenzophenone	1,3-Dimethylfluorenone	Aq. H₂SO₄	70	66
	2-Amino-2',4'-dimethylbenzophenone	1,4-Dimethylfluorenone	Aq. H₂SO₄	<50	54
	2-Amino-2',5'-dimethylbenzophenone	1,7-Dimethylfluorenone	Aq. H₂SO₄, Cu	58	102
	2-Amino-5,2'-dimethylbenzophenone	3,6-Dimethylfluorenone	Aq. H₂SO₄	70	101
$C_{16}H_{12}O_3$	2-Amino-4,5-dimethoxybenzophenone	2,3-Dimethoxyfluorenone	Aq. HCl	—	103
	2-Amino-3',4'-dimethoxybenzophenone	2,3-Dimethoxyfluorenone	Aq. HCl	60 crude	57
$C_{17}H_{10}O$	1-Benzoyl-2-naphthylamine	11-Chrysofluorenone	Aq. H₂SO₄	33	101
	1-(2'-Aminobenzoyl)naphthalene	11-Chrysofluorenone	CH₃CO₂H, H₂SO₄, Cu	25	75, 104
	3-Benzoyl-2-naphthylamine	11-Benzo[b]fluoren-11-one	Aq. HCl	13	75
	2-(2'-Aminobenzoyl)naphthalene	7-Benzo[c]fluoren-7-one	Aq. HCl	Traces	75
$C_{18}H_{10}O$	1-(2'-Aminobenzoyl)-2-methylnaphthalene	6-Methyl-7-benz[de]anthracene-7-one	Aq. HCl	10	76
$C_{19}H_{12}O_2$	1-(2'-Aminobenzoyl)-4-methoxynaphthalene	5-Methoxy-11-chrysofluorenone	Aq. HCl	55	57
$C_{21}H_{12}O$	3-(2'-Naphthoyl)-2-naphthylamine	12-Dibenzo[b,h]fluoren-12-one	Aq. HCl	20	75
$C_{23}H_{14}O_3$	1-Amino-2-(2',5'-dimethylbenzoyl)anthraquinone	9,12-Dimethyl-8-naphtho[2,3-c]fluoren-5,8,13-trione	Aq. H₂SO₄, Cu	25	105

Note: References 104–225 are listed on pp. 400–402.

* These yields are based on the isolated diazonium fluoborate; the other yields in the table are based on the amine.

TABLE IX

PHENANTHRIDONES

Numbering System for Phenanthridone
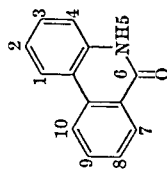
Product Formula	Starting Amine	Product	Procedure	Yield, %	Reference
$C_{11}H_6N_3O_5$	N-(2'-Aminobenzoyl)-3,5-dinitro-N-methylaniline	5-Methyl-1,3-dinitro-6(5)-phenanthridone	Acetone, Cu*	35	65
$C_{11}H_{10}BrNO$	N-(2'-Aminobenzoyl)-4-bromo-N-methylaniline	5-Methyl-2-bromo-6(5)-phenanthridone	Acetone, Cu*	33	196
$C_{11}H_{10}ClNO$	N-(2'-Aminobenzoyl)-4-chloro-N-methylaniline	5-Methyl-2-chloro-6(5)-phenanthridone	Acetone, Cu*	44	196
$C_{11}H_{10}N_2O_3$	N-(2'-Aminobenzoyl)-4-nitro-N-methylaniline	5-Methyl-2-nitro-6(5)-phenanthridone	Acetone, Cu*	28	65
$C_{11}H_{11}NO$	N-(2'-Aminobenzoyl)-N-methylaniline	5-Methyl-6(5)-phenanthridone	Aq. H_2SO_4	50	48
			Aq. H_2SO_4, Cu	50	48
			Aq. HCl	29	48, 197
			Aq. NaOH	11	48
			Dioxane, H_2SO_4, H_3PO_2, Cu	40	48
			Acetone, H_2SO_4, Cu	53	48
			Acetone, HBF_4, Cu*	50	48
			ArN_2BF_4, pet. ether	17	48
			Aq. H_2SO_4	50	64
$C_{15}H_{11}NO_3$	N-(2'-Amino-4',5'-methylenedioxybenzoyl)-N-methylaniline	5-Methyl-8,9-methylenedioxy-6(5)-phenanthridone	—		
$C_{15}H_{12}BrNO$	N-(2'-Aminobenzoyl)-4-bromo-N-ethylaniline	3-Bromo-5-ethyl-6(5)-phenanthridone	Acetone, Cu*	50	225
$C_{15}H_{13}NO$	N-(2'-Aminobenzoyl)-N-methyl-4-toluidine	2,5-Dimethyl-6(5)-phenanthridone	Aq. H_2SO_4 or acetone, Cu*	35	196
$C_{16}H_{13}NO_3$	N-(2'-Amino-1'carbomethoxybenzoyl)-N-methylanilino	5-Methyl-9-carbomethoxy-6(5)-phenanthridone			196
$C_{16}H_{15}NO$	N-(2'-Aminobenzoyl)-2,4,N-trimethylaniline	2,4,5-Trimethyl-6(5)-phenanthridone	Aq. HCl, Cu	10	66
	N-(2'-Aminobenzoyl)-4-methyl-N-ethylaniline	5-Ethyl-3-methyl-6(5)-phenanthridone	—		225
$C_{19}H_{11}NO$	N-(2'-Aminobenzoyl)carbazole	13-Indolo[3,2,1-de]phenanthridin-13-one			173
$C_{20}H_{15}NO$	N-(2'-Aminobenzoyl)-N-benzylaniline	5-Benzyl-6(5)-phenanthridone	Aq. H_2SO_4	54†	198
$C_{21}H_{15}NO$	N-(2'-Aminobenzoyl)-4-ethoxy-N-benzylaniline	5-Benzyl-2-ethoxy-6(5)-phenanthridone	Aq. acid		198
			—		

Note: References 104–225 are listed on pp. 460–462.

* The crystalline diazonium salt was used.

† The yield was the same in the presence or absence of copper.

TABLE X

APORPHINE DERIVATIVES

Numbering System for Aporphine
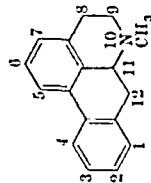
The *Chemical Abstracts* name is 6-methyl-5,6,6a,7-tetrahydro-4-dibenzo[de,g]quinoline, and the numbering starts at aporphine C5.

Product Formula	Starting Amine	Product	Procedure	Yield, %	Reference
$C_{17}H_{15}NO_2$	1-(2'-Aminobenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline	5,6-Methylenedioxynoraporphine	Aq. CH₃OH, H₂SO₄	22	50
$C_{17}H_{17}N$	1-(2'-Aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline	Aporphine	Aq. HCl, Cu	20	199
$C_{18}H_{17}NO_2$	1-(2'-Aminobenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline	5,6-Methylenedioxyaporphine	Aq. CH₃OH, H₂SO₄	24	50, 51
$C_{19}H_{15}NO_3$	1-(2'-Amino-4',5'-methylenedioxybenzoyl)-6,7-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	2,3,5,6-Bis-methylenedioxy-12-ketoaporphine	Aq. CH₃OH, H₂SO₄, Cu	30	200
$C_{19}H_{19}NO_3$	1-(2'-Amino-5'-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline	2-Methoxy-5,6-methylenedioxyaporphine	Aq. CH₃OH, H₂SO₄	20	201, 202
	1-(2'-Amino-4'-methoxybenzyl)-6,7-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	3-Methoxy-5,6-methylenedioxyaporphine	Aq. CH₃OH, H₂SO₄	24	201, 203
	1-(2'-Amino-3'-methoxybenzyl)-6,7-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	4-Methoxy-5,6-methylenedioxyaporphine	Aq. CH₃OH, H₂SO₄	15	204
$C_{19}H_{21}NO_2$	1-(2'-Amino-3',4'-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline	3,4-Dimethoxyaporphine	Aq. H₂SO₄, Cu	40	205, 21
	1-(2'-Aminobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline	5,6-Dimethoxyaporphine	Aq. CH₃OH, H₂SO₄	15	206
			Aq. H₂SO₄, Cu	10	206
			Aq. H₂SO₄, Cu	15	207
$C_{20}H_{21}NO_4$	1-(2'-Amino-4',5'-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline	2,3-Dimethoxy-5,6-methylenedioxyaporphine	Aq. CH₃CH, H₂SO₄	25	208, 209
	1-(2'-Amino-3',4'-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline	3,4-Dimethoxy-5,6-methylenedioxyaporphine		25	210
	1-(2'-Amino-4',5'-methylenedioxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline	5,6-Dimethoxy-2,3-methylenedioxyaporphine	Aq. H₂SO₄, Cu	25	210

Formula	Starting material	Product	Conditions	Yield (%)	Ref.
$C_{19}H_{21}NO_3$	1-(2'-Amino-3',4'-dimethoxybenzyl)-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline	3,4,6-Trimethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	—	211
	1-(2'-Amino-4'-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	3,5,6-Trimethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	24	212
$C_{21}H_{23}NO_5$	1-(2'-Amino-4',5'-methylenedioxybenzyl)-7-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	5-Ethoxy-6-methoxy-2,3-methylenedioxyaporphine	Aq. H$_2$SO$_4$, Cu	15	213
	1-(2'-Amino-4',5'-methylenedioxybenzyl)-6-ethoxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	6-Ethoxy-5-methoxy-2,3-methylenedioxyaporphine	Aq. H$_2$SO$_4$, Cu	20	214
$C_{21}H_{23}NO_5$	1-(2'-Amino-4',5'-dimethoxybenzoyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	2,3,5,6-Tetramethoxy-12-ketoaporphine	Aq. CH$_3$OH, H$_2$SO$_4$, Cu	30	200
$C_{21}H_{25}NO_4$	1-(2'-Amino-4',5'-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	2,3,5,6-Tetramethoxyaporphine (glaucine)	Aq. H$_2$SO$_4$, Cu	—	14, 55
	1-(2'-Amino-4',5'-dimethoxybenzyl)-5,6-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	2,3,6,7-Tetramethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	25	215
	1-(2'-Amino-3',4'-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	3,4,5,6-Tetramethoxyaporphine	Aq. H$_2$SO$_4$, Cu	35	216
	1-(2'-Amino-3',4'-dimethoxybenzyl)-5,6-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	3,4,6,7-Tetramethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	15	217
	1-(2'-Amino-3',(4'-dimethoxybenzyl)-5,6-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline		Aq. CH$_3$OH, H$_2$SO$_4$	25	215
$C_{23}H_{26}N_2O_4$	1-(2'-Amino-4'-acetamino-3'-methoxybenzyl)-5,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	3-Acetamino-4,5,6-trimethoxyaporphine	Aq. H$_2$SO$_4$, Cu	3	218
$C_{23}H_{28}N_2O_4$	1-(2'-Amino-4'-ethoxybenzyl)-6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline	3-Ethoxy-5,6-dimethoxy-10-ethylnoraporphine	Cu	11	219
$C_{22}H_{25}NO_4$	1-(2'-Amino-4'-ethoxy-5'-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	3-Ethoxy-2,5,6-trimethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	27 crude	220
	1-(2'-Amino-4',5'-dimethoxybenzyl)-7-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	5-Ethoxy-2,3,6-trimethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	20	220
$C_{23}H_{27}NO_4$	1-(2'-Amino-5'-ethoxy-4'-methoxybenzyl)-7-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	2,5-Diethoxy-3,6-dimethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	5–10	221
	1-(2'-Amino-5'-ethoxy-4'-methoxybenzyl)-6-ethoxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	2,6-Diethoxy-3,5-dimethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	10	221
	1-(2'-Amino-5'-ethoxy-4'-methoxybenzyl)-6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline	2-Ethoxy-3,5,6-trimethoxy-10-ethylnoraporphine	Aq. CH$_3$OH, H$_2$SO$_4$	23	222
	1-(2'-Amino-4'-ethoxy-5'-methoxybenzyl)-6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline	3-Ethoxy-2,5,6-trimethoxy-10-ethylnoraporphine	Aq. CH$_3$OH, H$_2$SO$_4$	22–24	222
$C_{24}H_{21}NO_4$	1-(2'-Amino-4,5-dimethoxybenzyl)-3,4-dihydroisoquinoline	6-Benzyloxy-3,4-dimethoxy-10,11-dehydronoraporphine	Aq. H$_2$SO$_4$, Cu	—	223
$C_{28}H_{31}NO_4$	1-(2'-Amino-4'-benzyloxy-5'-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	3-Benzyloxy-2,5,6-trimethoxyaporphine	Aq. CH$_3$OH, H$_2$SO$_4$	64 crude	224

References 104–225 are listed on pp. 460–462.

TABLE XI

Sultones and Sultams

Molecular Formula of Sultone	Corresponding Sulfonic Acid	Yield, %	Reference
$C_{12}H_6Cl_2O_3S$	4,5'-Dichloro-2'-hydroxybiphenyl-2-sulfonic acid	16*	49
$C_{12}H_7ClO_3S$	5'-Chloro-2'-hydroxybiphenyl-2-sulfonic acid	15	49
$C_{12}H_7ClO_3S$	5-Chloro-2'-hydroxybiphenyl-2-sulfonic acid	80	49
$C_{12}H_8O_3S$	2'-Hydroxybiphenyl-2-sulfonic acid	52	49
$C_{13}H_9ClO_3S$	5-Chloro-2'-hydroxy-5'-methylbiphenyl-2-sulfonic acid	46	49
$C_{16}H_{10}O_3S$	1-(2'-Sulfophenyl)-2-naphthol	50	49
$C_{16}H_{10}O_3S$	2-(2'-Sulfophenyl)-1-naphthol	32	49
$C_{17}H_{18}O_3S$	5'-tert-Amyl-2'-hydroxybiphenyl-2-sulfonic acid	23	49

Molecular Formula of Sultam	Sultams		
$C_{12}H_9NO_2S$	Sultam of 2'-amino-2-biphenylsulfonic acid	76†	52
$C_{13}H_{11}NO_2S$	Sultam of 2'-methylamino-2-biphenylsulfonic acid	80†	52
$C_{16}H_{11}NO_2S$	Sultam of 2-(2'-amino-1-naphthyl)-benzenesulfonic acid	90‡	52

* The sultones were all prepared by heating the diazonium salt in the presence of copper powder
† The sultam was prepared by heating the aqueous solution of the diazonium salt.
‡ The sultam was prepared by pyrolysis of the triazene in the presence of sodium hydroxide and copper powder.

References to Tables I-XI

104 Taylor and Hobson, J. Chem. Soc., 1936, 181.
105 Ruggli and Dinger, Helv. Chim. Acta, 24, 173 (1941).
106 Barber and Stickings, J. Chem. Soc., 1945, 167.
107 May and Mosettig, J. Org. Chem., 11, 627, 631 (1946).
108 Schofield and Swain, J. Chem. Soc., 1949, 2393.
109 Nylén, Ber., 53, 158 (1920).
110 May and Mosettig, J. Org. Chem., 11, 441 (1946).
111 Hey and Osbond, J. Chem. Soc., 1949, 3172.
112 Mosettig and Burger, J. Am. Chem. Soc., 52, 2988 (1930).
113 Konovalova, Yunusov, and Orekhov, Bull. soc. chim. France, [5] 6, 1479 (1939); J. Gen. Chem., U.S.S.R., 9, 1507 (1939) [C. A., 34, 2852 (1940)].
114 Werner and Scherrer, Ann., 322, 135 (1902).
115 May, J. Am. Chem. Soc., 69, 717 (1947).
116 Akin, Stamatoff, and Bogert, J. Am. Chem. Soc., 59, 1268 (1937).
117 Mayer and English, Ann., 417, 60 (1918).
118 Hill, Short, and Stromberg, J. Chem. Soc., 1937, 937.
119 Higginbottom, Hill, and Short, J. Chem. Soc., 1937, 263.
120 Hill, Short, Stromberg, and Wiles, J. Chem. Soc., 1937, 510.
121 Holmes, Lee, and Mooradian, J. Am. Chem. Soc., 69, 1998 (1947).
122 Knorr and Hörlein, Ber., 40, 2010 (1907).
123 Rapson and Robinson, J. Chem. Soc., 1935, 1541.
124 Akin and Bogert, J. Am. Chem. Soc., 59, 1564 (1937).
125 Shirai, J. Pharm. Soc. Japan, 63, 517 (1943) [C. A., 45, 3401 (1951)].
126 Knorr and Hörlein, Ber., 42, 3497 (1909).
127 Schlittler and Müller, Helv. Chim. Acta, 31, 1119 (1948).
128 Cassaday and Bogert, J. Am. Chem. Soc., 61, 3055 (1939).
129 Mayer and Oppenheimer, Ber., 51, 510 (1918).
130 Weitzenböck and Lieb, Monatsh., 33, 549 (1912).

[131] Kondo and Ochiai, *J. Pharm. Soc. Japan*, No. 539, 17 (1927) [*C. A.*, 22, 4531 (1928)]; *Ann.*, 470, 224 (1929).

[132] Goto and Sudzuki, *Bull. Chem. Soc. Japan*, 4, 163 (1929) [*C. A.*, 24, 122 (1930)].

[133a] Hewett and Martin, *J. Chem. Soc.*, 1940, 1396.

[133b] Wolf, *J. Am. Chem. Soc.*, 75, 2073 (1953).

[134] Cassaday and Bogert, *J. Am. Chem. Soc.*, 61, 2461 (1939).

[135] Sharp, *J. Chem. Soc.*, 1936, 1234.

[136] Buchanan, Cook, and Loudon, *J. Chem. Soc.*, 1944, 325.

[137] Rapoport, Williams, and Cisney, *J. Am. Chem. Soc.*, 73, 1414 (1951).

[138] Barton, Cook, and Loudon, *J. Chem. Soc.*, 1945, 176.

[139] Gulland and Virden, *J. Chem. Soc.*, 1928, 1478.

[140] Rapoport, Allen, and Cisney, *J. Am. Chem. Soc.*, 77, 670 (1955).

[141] Briggs and Wilson, *J. Chem. Soc.*, 1941, 500.

[142] Gulland and Virden, *J. Chem. Soc.*, 1928, 921.

[143] Späth and Tharrer, *Ber.*, 66, 583 (1933).

[144] Fieser and Kilmer, *J. Am. Chem. Soc.*, 62, 1354 (1940).

[145] Hewett, *J. Chem. Soc.*, 1938, 1286; 1940, 293.

[146] Rajagopalan, *Proc. Indian Acad. Sci.*, 13A, 566 (1941) [*C. A.*, 35, 7965 (1941)].

[147] Barger and Silberschmidt, *J. Chem. Soc.*, 1928, 2919.

[148] Cook and Stephenson, *J. Chem. Soc.*, 1949, 842.

[149] von Braun and Zobel, *Ber.*, 56, 2142 (1923).

[150] Cook, *J. Chem. Soc.*, 1933, 1592.

[151] Weitzenböck and Klinger, *Monatsh.*, 39, 315 (1918).

[152] Waldmann, Spiegel, and Kunz, *J. prakt. Chem.*, [2] 135, 1 (1932).

[153] Waldmann and Pitschak, *Ann.*, 527, 183 (1937).

[154] Hornig, *J. Am. Chem. Soc.*, 74, 4572 (1952).

[155] Cassaday and Bogert, *J. Am. Chem. Soc.*, 61, 3058 (1939).

[156] Windaus, Jensen, and Schramme, *Ber.*, 57, 1875 (1924).

[157] Tucker and Whalley, *J. Chem. Soc.*, 1952, 3187.

[158] Stubbs and Tucker, *J. Chem. Soc.*, 1954, 227.

[159] Hawkins and Tucker, *J. Chem. Soc.*, 1950, 3286.

[160] Tucker and Whalley, *J. Chem. Soc.*, 1949, 632.

[161] Stubbs and Tucker, *J. Chem. Soc.*, 1951, 2936.

[162] Beaton and Tucker, *J. Chem. Soc.*, 1952, 3870.

[163] Bremer, *Ann.*, 514, 279 (1934).

[164] Waldmann and Back, *Ann.*, 545, 52 (1940).

[165] Ullmann, Kogan, and Deletra, *Ann.*, 332, 82 (1904).

[166] Storrie and Tucker, *J. Chem. Soc.*, 1931, 2255.

[167] Campbell and MacLean, *J. Chem. Soc.*, 1942, 504.

[168] Ullmann and Illgen, *Ber.*, 47, 380 (1914).

[169] Hunter and Darling, *J. Am. Chem. Soc.*, 53, 4183 (1931).

[170] Macrae and Tucker, *J. Chem. Soc.*, 1933, 1520.

[171] Nelmes and Tucker, *J. Chem. Soc.*, 1933, 1523.

[172] Tucker, *J. Chem. Soc.*, 1926, 3033.

[173] Plant and Tomlinson, *J. Chem. Soc.*, 1932, 2188.

[174] Burton and Gibson, *J. Chem. Soc.*, 125, 2501 (1924).

[175] Preston and Tucker, *J. Chem. Soc.*, 1943, 659.

[176] McCombie, MacMillan, and Scarborough, *J. Chem. Soc.*, 1931, 529.

[177] Cullinane, *J. Chem. Soc.*, 1930, 2267.

[178] Graebe and Ullmann, *Ber.*, 29, 1876 (1896).

[179] Cullinane, Davies, and Davies, *J. Chem. Soc.*, 1936, 1435.

[180] Davies, James, Middleton, Porter, *J. Chem. Soc.*, 1955, 1565.

[181] Block, Jr., *J. Am. Chem. Soc.*, 72, 5641 (1950).

[182] Neumoyer and Amstutz, *J. Am. Chem. Soc.*, 66, 1680 (1944).

[183] Guyot and Granderye, *Bull. soc. chim. France*, [3] 33, 198 (1905).

[184] Haller and Guyot, *Bull. soc. chim. France*, [3] 25, 750 (1901).

[185] Ullmann and Broido, *Ber.*, **39**, 356 (1906).

[186] Huntress, Pfister, and Pfister, *J. Am. Chem. Soc.*, **64**, 2845 (1942).

[187] Ullmann and Mallett, *Ber.*, **31**, 1694 (1898).

[188] Chardonnens and Lienert, *Helv. Chim. Acta*, **32**, 2340 (1949).

[189] Chardonnens and Perriard, *Helv. Chim. Acta*, **28**, 593 (1945).

[190] Lifschitz, *Rec. trav. chim.*, **54**, 397 (1935).

[191] Chardonnens and Würmli, *Helv. Chim. Acta*, **29**, 922 (1946).

[192] Mulholland and Ward, *J. Chem. Soc.*, **1954**, 4676.

[193] Reichert, *Arch. Pharm.*, **270**, 551 (1932) [*C. A.*, **27**, 717 (1933)].

[194] Graebe, *Ber.*, **29**, 826 (1896).

[195] Schaarschmidt and Herzenberg, *Ber.*, **53**, 1807 (1920).

[196] Heacock and Hey, *J. Chem. Soc.*, **1952**, 4059.

[197] Pictet and Gonset, *Arch. sci. phys. nat. Genève*, [4] **3**, 37 (1897) (Chem. Zentr., **1897**, I, 413).

[198] Mitsuhashi, *J. Pharm. Soc. Japan*, **63**, 177 (1943) [*C. A.*, **45**, 628 (1951)].

[199] Gadamer, Oberlin, and Schoeler, *Arch. Pharm.*, **263**, 81 (1925).

[200] Schlittler and Lindenmann, *Helv. Chim. Acta*, **32**, 1880 (1949).

[201] Faltis, Wagner, Adler, *Ber.*, **77**, 686 (1944).

[202] Marion, *J. Am. Chem. Soc.*, **66**, 1125 (1944).

[203] Schlittler, *Helv. Chim. Acta*, **15**, 394 (1932).

[204] Barger and Schlittler, *Helv. Chim. Acta*, **15**, 381 (1932).

[205] Späth and Hromatka, *Ber.*, **62**, 325 (1929).

[206] Gulland and Haworth, *J. Chem. Soc.*, **1928**, 581.

[207] Haworth, Perkin, Jr., and Rankin, *J. Chem. Soc.*, **127**, 2018 (1925); **1926**, 29

[208] Gulland and Haworth, *J. Chem. Soc.*, **1928**, 1132.

[209] Späth and Hromatka, *Ber.*, **61**, 1334 (1928).

[210] Kitasato and Shishido, *Ann.*, **527**, 176 (1937).

[211] Gulland and Haworth, *J. Chem. Soc.*, **1928**, 2083.

[212] Goto, Ianba, and Nozaki, *Ann.*, **530**, 142 (1937).

[213] Shishido, *Bull. Chem. Soc. Japan*, **12**, 150 (1937) [*C. A.*, **31**, 5802 (1937)].

[214] Shishido, *Bull. Chem. Soc. Japan*, **12**, 419 (1937) [*C. A.*, **32**, 944 (1938)].

[215] Callow, Gulland, and Haworth, *J. Chem. Soc.*, **1929**, 658.

[216] Späth and Hromatka, *Ber.*, **61**, 1692 (1928).

[217] Gulland and Haworth, *J. Chem. Soc.*, **1928**, 1834.

[218] Robinson and Shinoda, *J. Chem. Soc.*, **1926**, 1987.

[219] Goto and Shishido, *Ann.*, **539**, 262 (1939).

[220] Manske, Charlesworth, and Ashford, *J. Am. Chem. Soc.*, **73**, 3751 (1951).

[221] Schlittler, *Ber.*, **66**, 988 (1933).

[222] Barger, Eisenbrand, Eisenbrand, and Schlittler, *Ber.*, **66**, 450 (1933).

[223] Kondo and Ishiwata, *Ber.*, **64**, 1533 (1931).

[224] Douglas and Gulland, *J. Chem. Soc.*, **1931**, 2893.

[225] Govindachari and Arumugam, *J. Sci. Ind. Research India*, **14B**, 250 (1955) [*C. A.*, **50**, 342 (1956)].

INDEX